






Review

# Mechanisms of Immunothrombosis by SARS-CoV-2

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**Abstract:** SARS-CoV-2 contains certain molecules that are related to the presence of immunothrombosis. Here, we review the pathogen and damage-associated molecular patterns. We also study the imbalance of different molecules participating in immunothrombosis, such as tissue factor, factors of the contact system, histones, and the role of cells, such as endothelial cells, platelets, and neutrophil extracellular traps. Regarding the pathogenetic mechanism, we discuss clinical trials, case-control studies, comparative and translational studies, and observational studies of regulatory or inhibitory molecules, more specifically, extracellular DNA and RNA, histones, sensors for RNA and DNA, as well as heparin and heparinoids. Overall, it appears that a network of cells and molecules identified in this axis is simultaneously but differentially affecting patients at different stages of COVID-19, and this is characterized by endothelial damage, microthrombosis, and inflammation.

**Keywords:** pathogen-associated molecular patterns; damage-associated molecular patterns; extracellular DNA; extracellular RNA; SARS-CoV-2; immunothrombosis

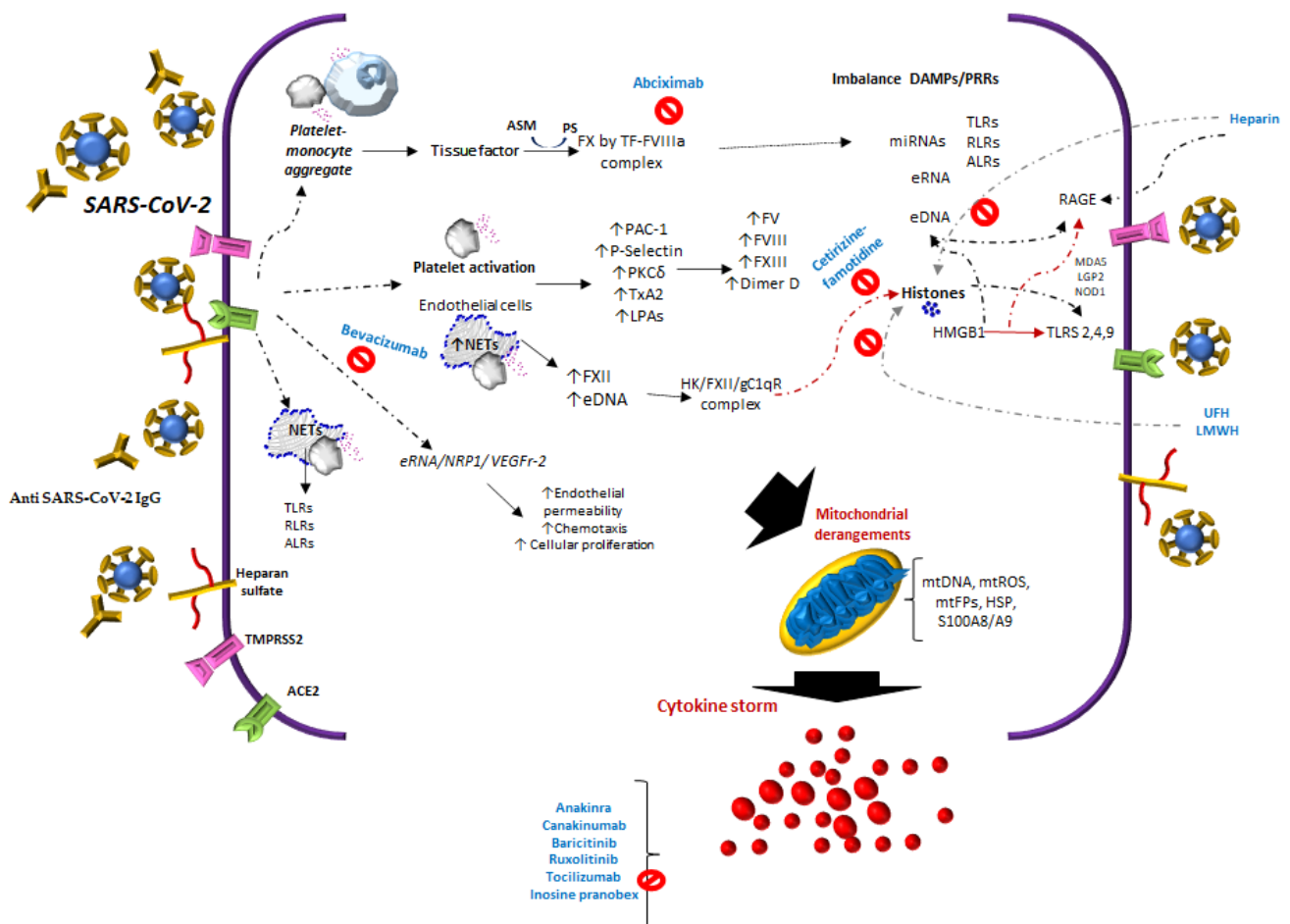
## 1. Introduction

In December 2019, the infectious outbreak of a new human coronavirus (SARS-CoV-2) responsible for acute respiratory syndrome was detected in Wuhan, China [1]. The WHO subsequently identified it as “the new novel coronavirus 2019”, or COVID-19 [2]. According to information available, SARS-CoV-2 has caused more than 235 million cases worldwide and more than 4 million deaths as of 5 October 2021 (<https://coronavirus.jhu.edu/map.html>) (accessed on 9 October 2021) [3]. Moreover, the scenario for 1 January 2022 is expected to exceed 5.8 million COVID-19 deaths globally [4].

COVID-19 shows heterogeneous clinical expression, which is associated with thrombosis and microangiopathy. There are various opposing theories related to the virus. On the one hand, it could be associated with intravascular coagulation [5]. On the other hand, it could correspond to complement-mediated thrombotic microangiopathies [6,7]. Hypercoagulation [8], platelet hyperactivity [9], and abnormal fibrinolysis [10,11] might explain

the diversity of macrovascular and microvascular thrombosis expression, depending on the study method. In the selection criteria for study subjects and the general population, the frequency of thrombosis is variable. For example, results from autopsies report that in 87% of microthrombosis cases [12], coagulopathy is found in up to 50% of fatalities [13], and macrothrombosis, such as deep vein thrombosis and pulmonary thromboembolism, is found in up to 40% [14,15].

Several signaling routes have been reported to play a role in the mechanisms of immunothrombosis or thrombo-inflammation [16,17] and cytokine storms in COVID-19 (Figure 1). The sequence of these events in SARS-CoV-2 infection is related to the interactions of different cells and molecules (Tables 1 and 2), such as Angiotensin-Converting Enzyme 2 (ACE2), tissue thromboplastin or tissue factor (TF), neutrophil extracellular traps (NETs), extracellular DNA (eDNA) and RNA, histones [18], anti-PF4/heparin IgG antibodies, antiphospholipid antibodies, neutrophil-platelet aggregates, and monocyte-platelet, among others.



**Figure 1.** The reported studies of COVID-19 infer that there are multiple activation or inhibition routes in platelets and endothelium, this involves the release of tissue thromboplastin (TF), with the participation of monocyte-platelet, neutrophil-platelet aggregates, complement-TF-NETs, and histones. In addition, to immune complexes SARS-CoV-2 spike/anti-spike IgG, anti-PF4/heparin IgG antibodies and antiphospholipid antibodies.

### 1.1. Factors of the Contact System

Recently, some molecules of the contact system (prekallikrein (PK), high-molecular-weight kininogen (HK), and factor XII (FXII)) have been reported to form an HK/FXII/gC1qR complex [19,20] which could participate in coagulation or inflammation. The gC1qR is a highly anionic multifunctional protein that participates in different mechanisms, including inflammation and vascular injury [21].

In COVID-19, specifically, the expression of FXIIa increases in lung tissue. In addition, this factor is colocalized with NETs in the lungs, indicating that the accumulation of NETs leads to greater activation of FXII due to a defect in the clearance of NETs by DNases, contributing to procoagulant activity [22]. This is also related to the activity of FXII in the blood coagulation system and increases in DNA and H4 histones [23]. Histones contribute to microvascular thrombosis and competitively inhibit plasmin to delay fibrinolysis [24].

Effects of factors of the contact system may also explain how coagulation, the kallikrein-kinin system, and inflammation molecules participate together as defense mechanisms favoring procoagulant mechanisms [25].

Clinical trials of this pathway of complement and kallikrein-kinin system activation use human recombinant C1 esterase inhibitor [26].

### 1.2. Tissue Factor

Factor III is a membrane protein that acts in the extrinsic pathway of coagulation, forming the FVIIa/TF complex [27]. The expression of tissue thromboplastin (also known as coagulation factor III), is a complex mechanism, a de-encryption of TF, which includes phospholipid scramblase and acid sphingomyelinase, i.e., the process transfers phosphatidylserine to the outer plasma membrane in monocytes for the efficient activation of FX by the TF-FVIIa complex [28]. Increases in TF release results in hypercoagulability and venous and arterial thromboembolism. TF is known to be released from different sources such as the alternative polarization macrophages [29] and microvesicles from endothelial cells [30]. The release of TF results from the formation of platelet-monocyte aggregates observed in severe COVID-19 [31]. Moreover, activated platelets induce NETs that carry FT [18]. In COVID-19, increased circulating extracellular vesicle TF activity has been reported, which correlates with the markers of thrombosis such as D-dimer [32]. It is important to point out that TF expression may be inhibited by platelet P-selectin (CD62P) neutralization or integrin  $\alpha$ IIb/ $\beta$ 3 blocking, as with abciximab [31].

### 1.3. Neutrophil Extracellular Traps and Molecule Release

Circulating neutrophils infected with SARS-CoV-2 release elevated levels of neutrophil-derived extracellular traps in the blood, trachea, and the lungs [33]. They also deliver all the contents of the nucleosomes, i.e., H2A, H2B, H3, and H4 histones, DNA [34], extracellular circulating viral micro-RNAs [35,36], and TF [25]. In COVID-19, the platelet/NETs/TF/thrombin axis is enhanced by complement activation [33]. Not only do neutrophils release eDNA, but also macrophages, eosinophils, and mast cells. These appear at different stages of thrombosis [37,38], and similarly in tumor cells [34].

In COVID-19 patients, platelet activation products, such as TXB2 and proteins from platelet  $\alpha$ -granules PF4/CXCL4 and PDGF, are also released and found in tracheal aspirates [31]. Furthermore, it has been found that NETs can serve as a platform for the activation of contact factors of the intrinsic coagulation pathway [22], such as FXII, FXI, and PK, in the lung parenchyma.

Of the molecules with NETs that are released, it has been suggested that free DNA may be the cause of a more severe pathology in COVID-19 [39]. Moreover, the manifestations of severity could be related not only to eDNA, but also to other alarmins, such as extracellular heat-shock proteins and HMGB1, mentioned above, in addition to diverse self-nucleic acids, including nuclear DNA, ribosomal RNA, extracellular RNA (eRNA), micro-RNAs, and histones [40], Figure 1.

NETs are cytotoxic and procoagulant, in part due to the release of DNA-histone complexes and double-stranded DNA, histones, and HMGB1 [41,42]. It is understood that the increase in DNA-binding proteins, extracellular ribosomal RNA, and micro-RNAs, may be related to thrombosis [43,44].

In COVID-19, eDNA from NETs and histones could also explain thrombosis in severe forms [45]. The half-life of eDNA is around 4–30 min [46]. Its clearance is regulated by different factors, such as 1) Serine proteases, e.g., Factor VII activating protease; cysteine proteases, e.g., caspase-activated DNase [47]; DNASE1; and deoxyribonuclease 1-like 3 (DNASE1L3) [48]. A deficiency in any of these nucleases causes the inability to remove blood clots [49]. 2) Receptors, such as those for advanced glycation end-products. In addition, Toll-like receptors 7 and 9 are sensors for eDNA in plasmacytoid dendritic cells (PDC) which have a huge capacity for producing type I (IFN- $\alpha$ ) and type III (IFN- $\lambda$ ) interferons; 100–1000 more than other cells [50]. Type III IFN shows greater activity against SARS-CoV-2 [51]. PDC and NK cells in the presence of interferon inducers, such as RNA-containing immune complexes, produce tumor necrosis factor - $\alpha$  (TNF- $\alpha$ ) and IL-6, among other pro-inflammatory cytokines, as in systemic lupus erythematosus. These cytokines are inhibited by interleukin -1 receptor-associated kinase 4 small molecule inhibitor, and also by hydroxychloroquine [52]. In addition, eRNA interacting with high affinity with vascular endothelial growth factor (VEGF) leads to the activation of VEGF-receptor 2/neuropilin-1 complex [42]. This complex increases endothelial permeability, chemotaxis, and cellular proliferation [53]. Moreover, some VEGF isoforms, such as the VEGF165 isoform, stimulate vascular growth and produce hyperpermeability. In order to block hyperpermeability in patients with severe COVID-19, clinical trials have been generated using bevacizumab as an anti-vascular endothelial growth factor [54,55].

A crucial point of NETs is the equilibrium or balance between the release of eDNA and eRNA and their respective nucleases, which are required to maintain homeostasis. In COVID-19, a significant increase in NETs is observed, and therefore an excess of eDNA. In clinical trials, the human DNase I enzyme, (Dornase Alpha) is being evaluated to reduce the severe symptoms of COVID-19 [56].

#### *1.4. Platelets-SARS-CoV-2/Angiotensin-Converting Enzyme 2*

Thrombocytopenia in COVID-19 is an indicator of poor prognosis, particularly when it decreases in the first 7 days after admission to the hospital. Thrombocytopenia is an independent risk factor associated with in-hospital mortality. Liu et al. [57] found that an increase of about  $50 \times 10^9$  /L over the whole range of platelet, decreases mortality. Adding support to the means of platelet activation, several studies show that platelets are activated in COVID-19 patients [58], i.e., there is an increase in young immature platelets named reticulated platelets (RPs). These are associated with high platelet turnover and arterial thrombotic events. In COVID-19, PRs or the immature platelet fraction (IPF) are similar to patients with acute myocardial infarction [59].

Considering that the expression of ACE2 and transmembrane protease serine 2 (TMPRSS2) on human platelets has been detected by immunoblotting, confocal microscopy [60], and flow cytometry [9], a controversial activation route takes into consideration platelet expression of ACE2 and TMPRSS2 receptors. Zhang et al. [9] showed that spike protein binds directly to ACE2, inducing platelet activation and potency in the presence of agonists such as thrombin. However, others such as Manne et al. [61] have detected platelets with mRNA from the SARS-CoV-2 N1 gene in COVID-19, but not the ACE2 receptor. These authors found changes in platelet gene expression and functions associated with ubiq-

uitination, antigen presentation, and mitochondrial dysfunction with increased MAPK pathway activation and thromboxane generation resulting in platelet hyperreactivity [61]. Zaid et al. [62] have also reported that SARS-CoV-2 RNA is associated with platelets similar to other viral infections, however they question the presence of the ACE2 receptor in platelets, due to the methods used to detect these receptors. Moreover, the platelets are the target of infection or capture the viral RNA. On the other hand, Shen et al. [63], using an immunofluorescence assay, flow cytometry analysis, quantitative analysis of SARS-CoV-2 RNA in culture, and Western blot, did not find ACE2 receptors in human platelets and megakaryocytes. In addition, they showed that SARS-CoV-2 could interact with platelets and megakaryocytes through an ACE2-independent mechanism.

Furthermore, platelets from subjects with severe forms of SARS-CoV-2 infection have increased expression of CD62P and release of thromboxane A2 [58], as well as the formation of platelet-neutrophil, platelet-monocyte, platelet-CD4 T cell, and platelet-CD8 T cell aggregates [61]. Platelets have a procoagulant phenotype [64] generated in the vascular circulation or megakaryocytes, which are affected by SARS-CoV-2 [65].

Platelet hyperactivity in COVID-19 can result from increased protein kinase C phosphorylation, the release of platelet extracellular vesicles, inflammatory cytokines PF4, TNF- $\alpha$ , IL-8, and IL-1 $\beta$  from platelets, inducing the formation of leukocyte-platelet aggregates [62,66].

In addition, platelets also participate with immune complexes or through other mechanisms, as indicated in Tables 1 and 2.

### 1.5. Heparin-Induced Thrombocytopenia

Considering that one of the main characteristics of COVID-19 is hypercoagulability, and therefore the increased risk of venous and arterial thrombosis, it is necessary to differentiate from Heparin-induced thrombocytopenia (HIT) [67–69], particularly secondary to the use of vaccines [70]. Uaprasert et al. [71], in a systematic review and meta-analysis, found a pooled incidence of HIT of 0.8%, being slightly higher in critically ill COVID-19 patients.

HIT is characterized by a decrease in platelets >30–50% associated with thromboembolic complications in around 50% of patients with confirmed HIT. This occurs between 5 and 14 days after starting heparin [72,73].

In the pathogenesis of HIT, antibodies that recognize complexes formed by platelet factor 4 (PF4) and polyanions, such as heparin [74] and anti-protamine (PRT)/heparin, are implicated [75]. These immunogenic complexes induce a response in which IgG bind to platelet Fc $\gamma$  RIIa receptors. This results in platelet hyperactivity, where they release circulating PF4-bearing microparticles [76], inducing the expression of TF by human monocytes [77] and the release of NETs [78].

HIT has some similarities to the novel disorder, named “vaccine-induced immune thrombotic thrombocytopenia”. For example, it starts 5–20 days after ChAdOx1 nCov-19 vaccination. The difference is that the neoantigen is formed by PF4 with components of the vaccine. Specifically, it is associated with an adenovirus hexon protein/ PF4 complex [79].

**Table 1.** Molecules, cells, complexes, or aggregates of importance in the generation of hypercoagulability and thrombosis.

Molecules, Cells, Complexes or Aggregates	Multiple Cells			Neutrophil Extracellular Traps and Histones		
	Tissue thromboplastin or TF release	Monocyte-platelet and neutrophil-platelet aggregates	Complement- TF-NETs	Remnants of NETs	Neutrophil-platelets	Histones
<b>Research Type</b>	Cross-sectional study and brief report using Dual RNA in situ hybridization and immunofluorescence	Comparative study	Clinical trial	Case-control study	Clinical trial	Translational study
<b>Study Characteristics</b>	66 patients with COVID-19 and 11 autopsies of lung tissues in patients with COVID-19 associated ARDS	37 patients with SARS-CoV-2 pneumonia and 28 healthy subjects	25 patients hospitalized with COVID-19 and 10 healthy age- and sex-matched individuals served as controls	44 patients hospitalized with COVID-19 who developed thrombosis, and gender- and age-matched COVID-19 patients without clinical thrombosis	36 patients with COVID-19 and 31 healthy controls were studied. Platelet and leukocyte activation, NETs and matrix metalloproteinase 9, a neutrophil-released enzyme, were measured	113 patients with COVID-19
<b>Key Findings</b>	Antithrombin/FVIIa complex and TF-containing microparticles were elevated in plasma of patients. TF expression correlated with SARS-CoV-2 staining, also, in regions close to TF, fibrin thrombi and thrombi positive for PF4 in COVID-19 versus non-COVID-19 ARDS lungs was found.	Circulating platelets from subjects with COVID-19 pneumonia show a phenotypic and functional profile of hypercoagulability and promote the activation of factors XII and VIII.	High levels of myeloperoxidase (MPO)/DNA complexes correlated with thrombin-antithrombin (TAT) Activity. Thrombin inhibition (dabigatran) or NETosis inhibition or C5aR1 (C5aRa/PMX-53) blockade decreased platelet-mediated NETs thrombogenicity.	Thrombosis in COVID-19 was associated with higher levels of cell-free DNA, myeloperoxidase-DNA complexes, and citrullinated histone H3 and calprotectin.	Platelet (P-selectin, soluble platelet P-selectin, Circulating CD66b+CD41+ platelet-neutrophil complexes) and neutrophil (neutrophil-derived microparticles, Myeloperoxidase (MPO)-DNA complexes) activation are key features of patients with COVID-19. NETs biomarkers may guide low-molecular-weight heparin treatment.	High levels of circulating histones (>30 µg/mL) in viral infection. Circulating histone levels were significantly higher in non-survivors than those who survived.
<b>Reference</b>	[80]	[64]	[18]	[81]	[82]	[83]

*Abbr:* Tissue factor (TF); neutrophil extracellular traps (NETs); acute respiratory distress syndrome (ARDS); platelet factor 4 (PF4).

**Table 2.** Molecules and complexes of importance in the generation of hypercoagulability and thrombosis.

Molecules and Complexes	SARS-CoV-2 Antibodies			
	SARS-CoV-2 spike/anti-spike IgG immune complexes	Anti-SARS-CoV-2 spike IgG immune complexes dependent on FcγRIIA	Anti-PF4/heparin IgG antibodies	Antiphospholipid antibodies
Research Type	In vitro experimental study using recombinant anti-spike IgG, platelet adhesion assay, light transmission aggregometry and flow cytometry.	In vitro experimental study using platelet adhesion assay, in-vitro thrombus formation, light transmission aggregometry, and flow cytometry measurement of fibrinogen binding.	Brief report/case analysis	Cross-sectional cohort study
Study Characteristics	SARS-CoV-2 S1 and anti-spike IgG immune complexes with different degrees of glycosylation were evaluated	Effects of low fucosylation and high galactosylation of anti spike IgG immune complex on platelet activation and thrombus formation on vWF were evaluated	12 COVID-19 patients with HIT	Serum samples from 172 hospitalized COVID-19 patients were evaluated for subtypes of aPL antibodies: aCL IgG, IgM, and IgA; anti-β2 glycoprotein I IgG, IgM, and IgA; and aPS/PT IgG and IgM. In addition, IgG purified from COVID-19 patient serum was injected into mouse models.
Key Findings	SARS-CoV-2/anti-spike IgG immune complexes increase platelet-mediated thrombosis if IgG expresses both low fucosylation and high galactosylation.	Immune complexes containing afucosylated IgG activate platelet FcγRIIA. Clustering of this platelet FcγRIIA could be inhibited by fostamatinib, ibrutinib or cangrelor that counteracted tyrosine kinases Syk, Btk or P2Y12 respectively.	Increased levels of anti-PF4/heparin antibodies, with negative platelet-activating antibodies.	52% of serum samples have antiphospholipid antibodies IgG fractions purified from serum of patients with COVID-19 could trigger aPL antibody-mediated prothrombotic NETs release and accelerate thrombosis in mouse by increased expression of NET remnants and citrullinated histone H3.
Reference	[9]	[84]	[85]	[86]

*Abbr:* Platelet factor 4 (PF4); heparin-induced thrombocytopenia (HIT); Antiphospholipid antibodies (aPL antibodies); anticardiolipin antibodies (aCL); anti-phosphatidylserine/prothrombin (aPS/PT); Platelets and peripheral blood mononuclear cells (PBMCs).

## 2. Cytokine Storm Syndrome

During a COVID-19 infection, immune cells flood the lungs and attack them instead of protecting them. The imbalance between PAMPs and pattern recognition receptors (PRRs) could fall into cytokine storm syndrome (CSS) or a specific syndrome from the family of conditions characterized by a cytokine storm such as macrophage activation syndrome. This is associated with autoimmune disorders, hemophagocytic lymphohistiocytosis genetic or secondary to different disorders, and cytokine release syndrome [87]. CSS is also associated with delayed secretion of type I and III interferons [88], and low levels thereof [89], probably due to membrane protein in SARS-CoV-2 via RIG-I/MDA-5-MAVS signaling [90]. Furthermore, CSS has hypercytokinemia [91], macrophage polarization from M2 to M1 [92], with activation of the *Plcγ2* pathway and a reduction in *Tmem178* levels in macrophages [93], T-cell cytotoxicity defects [16], complement activation [94], and increased NETs [95,96]. As a result of all these changes, patients suffer from hyperinflammation [97], cytokine release [98], cytokine storms [99,100], multiorgan disease [101], and thrombosis [15]. Therefore, various inhibitors have been suggested [102], several of which are being used in clinical trials. Some preliminary studies report a significant reduction in mortality, by Anakinra [103] and Canakinumab [104] for IL-1 inhibition, and baricitinib [105] and ruxolitinib [106] for JAK inhibition. However, others have divergent findings, e.g., tocilizumab [107,108] and sarilumab [109] for IL-6 inhibition (Figure 1). Moreover, molecules with immunomodulatory and antiviral properties that modulate cytokines and interferons in immunosuppressed subjects such as inosine pranobex [110,111] have been used in clinical trials with promising results [112].

## 3. Influence of Heparanase, Heparin and Heparinoids in Complications from COVID-19

Heparanase (HPSE) is an endo- $\beta$ -D-glucuronidase that has specificity for HS and heparin polysaccharide chains. It participates in the metabolism of HS in the extracellular matrix and its activity is modified in inflammation, cancer and cell migration [113]. Acting as a cofactor of TF, HPSE increases the activity of FX and interacts with the TF pathway inhibitor, acting as a procoagulant [114]. It also has platelet hyperactivity and thrombotic activity [115]. HPSE is increased in COVID-19 patients and is related to pathogenicity [116]. HPSE interacts with other molecules such as RNA, causing vascular leakage and inflammation. Low-molecular-weight heparins (LMWH) are potent inhibitors of HPSE, thrombus, and inflammation [101,117], and they also neutralize histones [118].

Histone levels together with HPSE levels may explain interindividual sensitivities to heparin (unfractionated heparin (UFH) and LMWH) or heparinoids in COVID-19 patients [119,120]. This means that the heparin used to treat microthrombosis in these subjects also participates in the inhibition of histones and could decrease its toxicity. The effect of LMWH is not always sufficient, as mentioned above, or it could be reversed [121]. In COVID-19 patients, the use of LMWH is very important due to its anticoagulant, antiviral, and anti-inflammatory effects [122]. However, the need for higher doses of LMWH has been observed in critically ill patients [123], and the use of oral anticoagulants is required, namely dabigatran, apixaban and rivaroxaban [124,125].

Heparin/ heparan sulphate competes with SARS-CoV-2 and reduces its entry into the body [126,127], because, in the SARSCoV-2 spike (S) protein, the receptor-binding domain (RBD) in the S1 subunit has an ectodomain that interacts with heparan sulfate (HS) [128], and the RBD region in S protein in SARS-CoV-2 interacts with 2-O or 6-O sulphate groups of heparin or enoxaparin [129]. Additionally, it has been reported that heparan sulphate inhibitors, such as mitoxantrone, sunitinib, and BNTX, could block entry of the virus [130]. In general, high negatively charged proteins, such as heparin, protein C, and pentraxin, neutralize histones [131]. Heparin has been shown to act directly against circulating histones, but its action does not depend on its anticoagulant function [132].

Among the heparin derivatives that have been proposed for the treatment of COVID-19 are heparinoids. Sulodexide is a heparinoid containing 80% iduronyl glycosaminoglycan sulphate (IGS) or fast-moving heparin and 20% dermatan sulphate (DS). IGS interacts with



and increases antithrombin and heparin cofactor II (HCII) [133], while DS interacts with HCII. This combination has properties resembling those of UFH [134]. Sulodexide also has profibrinolytic activity, which reduces the neo-synthesis of proinflammatory cytokines and inhibits histones [135]. It releases an inhibitor of the endothelial TF pathway, inhibiting FVIIa and FXa [136,137]. The prolonged use of sulodexide produces a “release and depletion” effect as observed with UFH [138]. Nevertheless, the use of heparin also has some limitations, such as its inability to inactivate antithrombin-heparin complex when it is bound to fibrin. Dermatan sulphate-HCII complex has been reported to inactivate fibrin-bound thrombin [139]. The RBD region in the S protein in SARS-CoV-2 interacts with 2-O or 6-O sulphate groups of heparin or enoxaparin [129]. Therefore, heparin, and most likely heparinoids, inhibit cellular interaction with the virus.

It is evident that, in addition to the factors related to the pathogenesis of SARS-CoV-2, other pathogenic factors are associated with thrombosis and inflammation, such as HPSE, eDNA, eRNA, micro-RNAs, and histones. Many of these molecules are being studied in order to find drugs to treat COVID-19.

#### 4. Conclusions

During COVID-19 infection, SARS-Cov-2 interacts with ACE2, NRP1, endothelial cells, platelets, NETs, thrombin, eDNA, and histones, inducing heterogeneous clinical manifestations characterized by endothelial damage, microthrombosis, and inflammation. In summary, a network of cells and molecules identified in this axis are simultaneously but differentially affecting COVID-19 patients at different stages of the disease.

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#### References

1. Lu, R.; Zhao, X.; Li, J.; Niu, P.; Yang, B.; Wu, H.; Wang, W.; Song, H.; Huang, B.; Zhu, N.; et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* **2020**, *395*, 565–574. [CrossRef]
2. WHO. World Health Organization. Laboratory Testing for 2019 Novel Coronavirus (2019-nCoV) in Suspected Human Cases. Available online: <https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117> (accessed on 13 August 2021).
3. Dong, E.; Du, H.; Gardner, L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect. Dis.* **2020**, *20*, e215. [CrossRef]
4. IHME. Institute for Health Metrics and Evaluation. Population Health Building/Hans Rosling Center. 2020 University of Washington. Available online: <https://covid19.healthdata.org/global?view=total-deaths&tab=trend> (accessed on 12 September 2021).
5. Levi, M.; Thachil, J. Coronavirus Disease 2019 Coagulopathy: Disseminated Intravascular Coagulation and Thrombotic Microangiopathy—Either, Neither, or Both. *Semin. Thromb. Hemost.* **2020**, *46*, 781–784. [CrossRef]
6. Gavriilaki, E.; Brodsky, R.A. Severe COVID-19 infection and thrombotic microangiopathy: Success does not come easily. *Br. J. Haematol.* **2020**, *189*, e227–e230. [CrossRef] [PubMed]
7. Falter, T.; Rossmann, H.; Menge, P.; Goetje, J.; Groenwoldt, S.; Weinmann, A.; Sivanathan, V.; Schulz, A.; Lemmermann, N.A.W.; Danckwardt, S.; et al. No Evidence for Classic Thrombotic Microangiopathy in COVID-19. *J. Clin. Med.* **2021**, *10*, 671. [CrossRef]

8. Venter, C.; Bezuidenhout, J.A.; Laubscher, G.J.; Lourens, P.J.; Steenkamp, J.; Kell, D.B.; Pretorius, E. Erythrocyte, Platelet, Serum Ferritin, and P-Selectin Pathophysiology Implicated in Severe Hypercoagulation and Vascular Complications in COVID-19. *Int. J. Mol. Sci.* **2020**, *21*, 8234. [[CrossRef](#)] [[PubMed](#)]
9. Zhang, S.; Liu, Y.; Wang, X.; Yang, L.; Li, H.; Wang, Y.; Liu, M.; Zhao, X.; Xie, Y.; Yang, Y.; et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *J. Hematol. Oncol.* **2020**, *13*, 120. [[CrossRef](#)] [[PubMed](#)]
10. Wright, F.L.; Vogler, T.O.; Moore, E.E.; Moore, H.B.; Wohlaer, M.V.; Urban, S.; Nydam, T.L.; Moore, P.K.; McIntyre, R.C., Jr. Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. *J. Am. Coll. Surg.* **2020**, *231*, 193–203. [[CrossRef](#)]
11. Bachler, M.; Bösch, J.; Stürzel, D.P.; Hell, T.; Giebl, A.; Ströhle, M.; Klein, S.J.; Schäfer, V.; Lehner, G.F.; Joannidis, M.; et al. Impaired fibrinolysis in critically ill COVID-19 patients. *Br. J. Anaesth.* **2021**, *126*, 590–598. [[CrossRef](#)]
12. Carsana, L.; Sonzogni, A.; Nasr, A.; Rossi, R.S.; Pellegrinelli, A.; Zerbi, P.; Rech, R.; Colombo, R.; Antinori, S.; Corbellino, M.; et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: A two-centre descriptive study. *Lancet Infect. Dis.* **2020**, *20*, 1135–1140. [[CrossRef](#)]
13. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* **2020**, *395*, 1038. [[CrossRef](#)]
14. Asakura, H.; Ogawa, H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int. J. Hematol.* **2021**, *113*, 45–57. [[CrossRef](#)] [[PubMed](#)]
15. Miesbach, W.; Makris, M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. *Clin. Appl. Thromb. Hemost.* **2020**, *26*, 1076029620938149. [[CrossRef](#)] [[PubMed](#)]
16. Beristain-Covarrubias, N.; Perez-Toledo, M.; Thomas, M.R.; Henderson, I.R.; Watson, S.P.; Cunningham, A.F. Understanding Infection-Induced Thrombosis: Lessons Learned From Animal Models. *Front. Immunol.* **2019**, *10*, 2569. [[CrossRef](#)] [[PubMed](#)]
17. Jayarangaiah, A.; Kariyanna, P.T.; Chen, X.; Jayarangaiah, A.; Kumar, A. COVID-19-Associated Coagulopathy: An Exacerbated Immunothrombosis Response. *Clin. Appl. Thromb. Hemost.* **2020**, *26*, 1076029620943293. [[CrossRef](#)] [[PubMed](#)]
18. Skendros, P.; Mitsios, A.; Chrysanthopoulou, A.; Mastellos, D.C.; Metallidis, S.; Rafailidis, P.; Ntinopoulou, M.; Sertaridou, E.; Tsironidou, V.; Tsigalou, C.; et al. Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. *J. Clin. Investig.* **2020**, *130*, 6151–6157. [[CrossRef](#)]
19. Kaira, B.G.; Slater, A.; McCrae, K.R.; Dreveny, I.; Sumya, U.; Mutch, N.J.; Searle, M.; Emsley, J. Factor XII and kininogen asymmetric assembly with gC1qR/C1QBP/P32 is governed by allostery. *Blood* **2020**, *136*, 1685–1697. [[CrossRef](#)] [[PubMed](#)]
20. Tucker, E.I. Crystalizing our view of the contact system. *Blood* **2020**, *136*, 1576–1577.
21. Peerschke, E.I.; Ghebrehiwet, B. Human blood platelet gC1qR/p33. *Immunol. Rev.* **2001**, *180*, 56–64. [[CrossRef](#)]
22. Englert, H.; Rangaswamy, C.; Deppermann, C.; Sperhake, J.P.; Krisp, C.; Schreier, D.; Gordon, E.; Konrath, S.; Haddad, M.; Pula, G.; et al. Defective NET clearance contributes to sustained FXII activation in COVID-19-associated pulmonary thrombo-inflammation. *EBioMedicine* **2021**, *67*, 103382. [[CrossRef](#)]
23. Reyes-García, A.M.L.; Aroca, A.; Arroyo, A.B.; García-Barbera, N.; Vicente, V.; González-Conejero, R.; Martínez, C. Neutrophil extracellular trap components increase the expression of coagulation factors. *Biomed. Rep.* **2019**, *10*, 195–201. [[PubMed](#)]
24. Locke, M.; Longstaff, C. Extracellular Histones Inhibit Fibrinolysis through Noncovalent and Covalent Interactions with Fibrin. *Thromb. Haemost.* **2021**, *121*, 464–476. [[PubMed](#)]
25. Shatzel, J.J.; DeLoughery, E.P.; Lorentz, C.U.; Tucker, E.I.; Aslan, J.E.; Hinds, M.T.; Gailani, D.; Weitz, J.I.; McCarty, O.J.T.; Gruber, A. The contact activation system as a potential therapeutic target in patients with COVID-19. *Res. Pract. Thromb. Haemost.* **2020**, *4*, 500–505. [[CrossRef](#)]
26. Urwyler, P.; Moser, S.; Charitos, P.; Heijnen, I.A.F.M.; Rudin, M.; Sommer, G.; Giannetti, B.M.; Bassetti, S.; Sendi, P.; Trendelenburg, M.; et al. Treatment of COVID-19 With Conestat Alfa, a Regulator of the Complement, Contact Activation and Kallikrein-Kinin System. *Front. Immunol.* **2020**, *11*, 2072. [[CrossRef](#)]
27. Zelaya, H.; Rothmeier, A.S.; Ruf, W. Tissue factor at the crossroad of coagulation and cell signaling. *J. Thromb. Haemost.* **2018**, *16*, 1941–1952. [[CrossRef](#)]
28. Grover, S.P.; Mackman, N. Tissue Factor: An Essential Mediator of Hemostasis and Trigger of Thrombosis. *Arter. Thromb. Vasc. Biol.* **2018**, *38*, 709–725. [[CrossRef](#)]
29. Hohensinner, P.J.; Mayer, J.; Kichbacher, J.; Kral-Pointner, J.; Thaler, B.; Kaun, C.; Hell, L.; Haider, P.; Mussbacher, M.; Schmid, J.A.; et al. Alternative activation of human macrophages enhances tissue factor expression and production of extracellular vesicles. *Haematologica* **2021**, *106*, 454–463. [[CrossRef](#)] [[PubMed](#)]
30. Arderiu, G.; Peña, E.; Badimon, L. Ischemic tissue released microvesicles induce monocyte reprogramming and increase tissue repair by a tissue factor-dependent mechanism. *Cardiovasc. Res.* **2021**. [[CrossRef](#)]
31. Hottz, E.D.; Azevedo-Quintanilha, I.G.; Palhinha, L.; Teixeira, L.; Barreto, E.A.; Pão, C.R.R.; Righy, C.; Franco, S.; Souza, T.M.L.; Kurtz, P.; et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. *Blood* **2020**, *136*, 1330–1341. [[CrossRef](#)]
32. Rosell, A.; Havervall, S.; von Meijenfeldt, F.; Hisada, Y.; Aguilera, K.; Grover, S.P.; Lisman, T.; Mackman, N.; Thälén, C. Patients With COVID-19 Have Elevated Levels of Circulating Extracellular Vesicle Tissue Factor Activity That Is Associated With Severity and Mortality—Brief Report. *Arter. Thromb. Vasc. Biol.* **2021**, *41*, 878–882. [[CrossRef](#)] [[PubMed](#)]

33. Veras, F.P.; Pontelli, M.C.; Silva, C.M.; Toller-Kawahisa, J.E.; de Lima, M.; Nascimento, D.C.; Schneider, A.H.; Caetité, D.; Tavares, L.A.; Paiva, I.M.; et al. SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology. *J. Exp. Med.* **2020**, *217*, e20201129. [[CrossRef](#)] [[PubMed](#)]
34. Tan, S.; Davey, C.A. Nucleosome structural studies. *Curr. Opin. Struct. Biol.* **2011**, *21*, 128–136. [[CrossRef](#)] [[PubMed](#)]
35. Laganà, A.; Russo, F.; Veneziano, D.; Bella, S.D.; Giugno, R.; Pulvirenti, A.; Croce, C.M.; Ferro, A. Extracellular circulating viral microRNAs: Current knowledge and perspectives. *Front. Genet.* **2013**, *4*, 120. [[CrossRef](#)]
36. Sohel, M.H. Extracellular/Circulating MicroRNAs: Release Mechanisms, Functions and Challenges. *Achiev. Life Sci.* **2016**, *10*, 175–186. [[CrossRef](#)]
37. Daniel, C.; Leppkes, M.; Muñoz, L.E.; Schley, G.; Schett, G.; Herrmann, M. Extracellular DNA traps in inflammation, injury and healing. *Nat. Rev. Nephrol.* **2019**, *15*, 559–575. [[CrossRef](#)]
38. Pertiwi, K.R.; de Boer, O.J.; Mackaaij, C.; Pabittei, D.R.; de Winter, R.J.; Li, X.; van der Wal, A.C. Extracellular traps derived from macrophages, mast cells, eosinophils and neutrophils are generated in a time-dependent manner during atherothrombosis. *J. Pathol.* **2019**, *247*, 505–512. [[CrossRef](#)]
39. Liu, B. Free DNA, a reason for severe COVID-19 infection? *Med. Hypotheses* **2020**, *142*, 109812. [[CrossRef](#)]
40. Preissner, K.T.; Fischer, S.; Deindl, E. Extracellular RNA as a Versatile DAMP and Alarm Signal That Influences Leukocyte Recruitment in Inflammation and Infection. *Front. Cell Dev. Biol.* **2020**, *8*, 619221. [[CrossRef](#)]
41. Liaw, P.C.; Ito, T.; Iba, T.; Thachil, J.; Zeerleder, S. D.DAMP and DIC: The role of extracellular DNA and DNA-binding proteins in the pathogenesis of DIC. *Blood Rev.* **2016**, *30*, 257–261. [[CrossRef](#)]
42. Kim, J.E.; Lee, N.; Gu, J.Y.; Yoo, H.J.; Kim, H.K. Circulating levels of DNA-histone complex and dsDNA are independent prognostic factors of disseminated intravascular coagulation. *Thromb. Res.* **2015**, *135*, 1064–1069. [[CrossRef](#)]
43. Vijay, A.; Jha, P.K.; Garg, I.; Sharma, M.; Ashraf, M.Z.; Kumar, B. micro-RNAs dependent regulation of DNMT and HIF1 $\alpha$  gene expression in thrombotic disorders. *Sci. Rep.* **2019**, *9*, 4815. [[CrossRef](#)]
44. Zerneck, A.; Preissner, K.T. Extracellular Ribonucleic Acids (RNA) Enter the Stage in Cardiovascular Disease. *Circ. Res.* **2016**, *118*, 469–479. [[CrossRef](#)] [[PubMed](#)]
45. Fuchs, T.A.; Brill, A.; Duerschmied, D.; Schatzberg, D.; Monestier, M.; Myers, D.D., Jr.; Wroblewski, S.K.; Wakefield, T.W.; Hartwig, J.H.; Wagner, D.D. Extracellular DNA traps promote thrombosis. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 15880–15885. [[CrossRef](#)] [[PubMed](#)]
46. Lo, Y.M.; Zhang, J.; Leung, T.N.; Lau, T.K.; Chang, A.M.; Hjelm, N.M. Rapid clearance of fetal DNA from maternal plasma. *Am. J. Hum. Genet.* **1999**, *64*, 218–224. [[CrossRef](#)] [[PubMed](#)]
47. Larsen, B.D.; Sørensen, C.S. The caspase-activated DNase: Apoptosis and beyond. *FEBS J.* **2017**, *284*, 1160–1170. [[CrossRef](#)] [[PubMed](#)]
48. Jiménez-Alcázar, M.; Rangaswamy, C.; Panda, R.; Bitterling, J.; Simsek, Y.J.; Long, A.T.; Bilyy, R.; Krenn, V.; Renné, C.; Renné, T.; et al. Host DNases prevent vascular occlusion by neutrophil extracellular traps. *Science* **2017**, *358*, 1202–1206. [[CrossRef](#)] [[PubMed](#)]
49. Lauková, L.; Konečná, B.; Janovičová, L.; Vlčková, B.; Celec, P. Deoxyribonucleases and Their Applications in Biomedicine. *Biomolecules* **2020**, *10*, 1036. [[CrossRef](#)]
50. Guiducci, C.; Coffman, R.L.; Barrat, F.J. Signalling pathways leading to IFN- $\alpha$  production in human plasmacytoid dendritic cell and the possible use of agonists or antagonists of TLR7 and TLR9 in clinical indications. *J. Intern. Med.* **2009**, *265*, 43–57. [[CrossRef](#)]
51. Jafarzadeh, A.; Nemati, M.; Saha, B.; Bansode, Y.D.; Jafarzadeh, S. Protective Potentials of Type III Interferons in COVID-19 Patients: Lessons from Differential Properties of Type I- and III Interferons. *Viral Immunol.* **2021**, *34*, 307–320. [[CrossRef](#)]
52. Hjorton, K.; Hagberg, N.; Israelsson, E.; Jinton, L.; Berggren, O.; Sandling, J.K.; Thörn, K.; Mo, J.; The DISSECT Consortium; Eloranta, M.L.; et al. Cytokine production by activated plasmacytoid dendritic cells and natural killer cells is suppressed by an IRAK4 inhibitor. *Arthritis Res.* **2018**, *20*, 238. [[CrossRef](#)]
53. Becker, P.M.; Waltenberger, J.; Yachechko, R.; Mirzapourzadeh, T.; Sham, J.S.; Lee, C.G.; Elias, J.A.; Verin, A.D. Neuropilin-1 regulates vascular endothelial growth factor-mediated endothelial permeability. *Circ. Res.* **2005**, *96*, 1257–1265. [[CrossRef](#)] [[PubMed](#)]
54. Fantin, A.; Lampropoulou, A.; Senatore, V.; Brash, J.T.; Prahst, C.; Lange, C.A.; Liyanage, S.E.; Raimondi, C.; Bainbridge, J.W.; Augustin, H.G.; et al. VEGF165-induced vascular permeability requires NRP1 for ABL-mediated SRC family kinase activation. *J. Exp. Med.* **2017**, *214*, 1049–1064. [[CrossRef](#)]
55. Pang, J.; Xu, F.; Aondio, G.; Li, Y.; Fumagalli, A.; Lu, M.; Valmadre, G.; Wei, J.; Bian, Y.; Canesi, M.; et al. Efficacy and tolerability of bevacizumab in patients with severe Covid-19. *Nat. Commun.* **2021**, *12*, 814. [[CrossRef](#)]
56. Okur, H.K.; Yalcin, K.; Tastan, C.; Demir, S.; Yurtsever, B.; Karakus, G.S.; Kancagi, D.D.; Abanuz, S.; Seyis, U.; Zengin, R.; et al. Preliminary report of in vitro and in vivo effectiveness of dornase alfa on SARS-CoV-2 infection. *New Microbes New Infect.* **2020**, *37*, 100756. [[CrossRef](#)]
57. Liu, Y.; Sun, W.; Guo, Y.; Chen, L.; Zhang, L.; Zhao, S.; Long, D.; Yu, L. Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. *Platelets* **2020**, *31*, 490–496. [[CrossRef](#)]
58. Campbell, R.A.; Boilard, E.; Rondina, M.T. Is there a role for the ACE2 receptor in SARS-CoV-2 interactions with platelets? *J. Thromb. Haemost.* **2021**, *19*, 46–50. [[CrossRef](#)]

59. Cohen, A.; Harari, E.; Cipok, M.; Laish-Farkash, A.; Bryk, G.; Yahud, E.; Sela, Y.; Lador, N.K.; Mann, T.; Mayo, A.; et al. Immature platelets in patients hospitalized with Covid-19. *J. Thromb. Thrombolysis* **2021**, *51*, 608–616. [[CrossRef](#)]
60. Sahai, A.; Bhandari, R.; Koupenova, M.; Freedman, J.; Godwin, M.; McIntyre, T.; Chung, M.; Iskandar, J.P.; Kamran, H.; Aggarwal, A.; et al. SARS-CoV-2 Receptors are Expressed on Human Platelets and the Effect of Aspirin on Clinical Outcomes in COVID-19 Patients. *Res. Sq.* **2020**, *3*. [[CrossRef](#)]
61. Manne, B.K.; Denorme, F.; Middleton, E.A.; Portier, I.; Rowley, J.W.; Stubben, C.; Petrey, A.C.; Tolley, N.D.; Guo, L.; Cody, M.; et al. Platelet gene expression and function in patients with COVID-19. *Blood* **2020**, *136*, 1317–1329. [[CrossRef](#)] [[PubMed](#)]
62. Zaid, Y.; Puhm, F.; Allaey, I.; Naya, A.; Oudghiri, M.; Khalki, L.; Limami, Y.; Zaid, N.; Sadki, K.; Ben El Haj, R.; et al. Platelets Can Associate with SARS-Cov-2 RNA and Are Hyperactivated in COVID-19. *Circ. Res.* **2020**, *127*, 1404–1418. [[CrossRef](#)] [[PubMed](#)]
63. Shen, S.; Zhang, J.; Fang, Y.; Lu, S.; Wu, J.; Zheng, X.; Deng, F. SARS-CoV-2 interacts with platelets and megakaryocytes via ACE2-independent mechanism. *J. Hematol. Oncol.* **2021**, *14*, 72. [[CrossRef](#)]
64. Taus, F.; Salvagno, G.; Canè, S.; Fava, C.; Mazzaferri, F.; Carrara, E.; Petrova, V.; Barouni, R.M.; Dima, F.; Dalbeni, A.; et al. Platelets Promote Thromboinflammation in SARS-CoV-2 Pneumonia. *Arter. Thromb. Vasc. Biol.* **2020**, *40*, 2975–2989. [[CrossRef](#)] [[PubMed](#)]
65. Bernardes, J.P.; Mishra, N.; Tran, F.; Bahmer, T.; Best, L.; Blasé, J.I.; Bordoni, D.; Franzenburg, J.; Geisen, U.; Josephs-Spaulding, J.; et al. Longitudinal Multi-omics Analyses Identify Responses of Megakaryocytes, Erythroid Cells, and Plasmablasts as Hallmarks of Severe COVID-19. *Immunity* **2020**, *53*, 1296–1314. [[CrossRef](#)] [[PubMed](#)]
66. von Meijenfeldt, F.A.; Havervall, S.; Adelmeijer, J.; Lundström, A.; Magnusson, M.; Mackman, N.; Thalín, C.; Lisman, T. COVID-19 is Associated with an Acquired Factor XIII Deficiency. *Thromb. Haemost.* **2021**. Epub ahead of print. [[CrossRef](#)]
67. Sartori, M.; Cosmi, B. Heparin-induced thrombocytopenia and COVID-19. *Hematol. Rep.* **2021**, *13*, 8857. [[CrossRef](#)] [[PubMed](#)]
68. Lingamaneni, P.; Gonakoti, S.; Moturi, K.; Vohra, I.; Zia, M. Heparin-Induced Thrombocytopenia in COVID-19. *J. Investig. Med. High Impact Case Rep.* **2020**, *8*, 2324709620944091.
69. Daviet, F.; Guervilly, C.; Baldesi, O.; Bernard-Guervilly, F.; Pilarczyk, E.; Genin, A.; Lefebvre, L.; Forel, J.M.; Papazian, L.; Camoin-Jau, L. Heparin-Induced Thrombocytopenia in Severe COVID-19. *Circulation* **2020**, *142*, 1875–1877. [[CrossRef](#)]
70. Warkentin, T.E.; Kaatz, S. COVID-19 versus HIT hypercoagulability. *Thromb. Res.* **2020**, *196*, 38–51. [[CrossRef](#)]
71. Uaprasert, N.; Tangcheewinsirikul, N.; Rojnuckarin, P.; Patell, R.; Zwicker, J.I.; Chiasakul, T. Heparin-induced Thrombocytopenia in Patients with Coronavirus Disease 2019: Systematic Review and Meta-analysis. *Blood Adv.* **2021**. [[CrossRef](#)]
72. Greinacher, A.; Füllrill, B.; Selleng, S. Heparin-induced thrombocytopenia. *Methods Mol. Biol.* **2013**, *992*, 301–318.
73. Arepally, G.M.; Cines, D.B. Pathogenesis of heparin-induced thrombocytopenia. *Transl. Res.* **2020**, *225*, 131–140. [[CrossRef](#)] [[PubMed](#)]
74. Arepally, G.M.; Kamei, S.; Park, K.S.; Kamei, K.; Li, Z.Q.; Liu, W.; Siegel, D.L.; Kisiel, W.; Cines, D.B.; Poncz, M. Characterization of a murine monoclonal antibody that mimics heparin-induced thrombocytopenia antibodies. *Blood* **2000**, *95*, 1533–1540. [[CrossRef](#)] [[PubMed](#)]
75. Lee, G.M.; Joglekar, M.; Kuchibhatla, M.; Khandelwal, S.; Qi, R.; Rauova, L.; Arepally, G.M. Serologic characterization of anti-protamine/heparin and anti-PF4/heparin antibodies. *Blood Adv.* **2017**, *1*, 644–651. [[CrossRef](#)] [[PubMed](#)]
76. Campello, E.; Radu, C.M.; Duner, E.; Lombardi, A.M.; Spiezia, L.; Bendo, R.; Ferrari, S.; Simioni, P.; Fabris, F. Activated Platelet-Derived and Leukocyte-Derived Circulating Microparticles and the Risk of Thrombosis in Heparin-Induced Thrombocytopenia: A Role for PF4-Bearing Microparticles? *Cytom. B Clin. Cytom.* **2018**, *94*, 334–341. [[CrossRef](#)] [[PubMed](#)]
77. Lhermusier, T.; van Rottem, J.; Garcia, C.; Xuereb, J.M.; Ragab, A.; Martin, V.; Gratacap, M.P.; Sié, P.; Payrastre, B. The Syk-kinase inhibitor R406 impairs platelet activation and monocyte tissue factor expression triggered by heparin-PF4 complex directed antibodies. *J. Thromb. Haemost.* **2011**, *9*, 2067–2076. [[CrossRef](#)]
78. Perdomo, J.; Leung, H.H.L.; Ahmadi, Z.; Yan, F.; Chong, J.J.H.; Passam, F.H.; Chong, B.H. Neutrophil activation and NETosis are the major drivers of thrombosis in heparin-induced thrombocytopenia. *Nat. Commun.* **2019**, *10*, 1322. [[CrossRef](#)]
79. Greinacher, A.; Selleng, K.; Palankar, R.; Wesche, J.; Handtke, S.; Wolff, M.; Aurich, K.; Lalk, M.; Methling, K.; Volker, U.; et al. Insights in ChAdOx1 nCov-19 Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT). *Blood* **2021**. [[CrossRef](#)]
80. Francischetti, I.M.B.; Toomer, K.; Zhang, Y.; Jani, J.; Siddiqui, Z.; Brotman, D.J.; Hooper, J.E.; Kickler, T.S. Upregulation of pulmonary tissue factor, loss of thrombomodulin and immunothrombosis in SARS-CoV-2 infection. *EClinicalMedicine* **2021**, *39*, 101069. [[CrossRef](#)] [[PubMed](#)]
81. Zuo, Y.; Zuo, M.; Yalavarthi, S.; Gockman, K.; Madison, J.A.; Shi, H.; Woodard, W.; Lezak, S.P.; Lugogo, N.L.; Knight, J.S.; et al. Neutrophil extracellular traps and thrombosis in COVID-19. *J. Thromb. Thrombolysis* **2021**, *51*, 446–453. [[CrossRef](#)]
82. Petito, E.; Falcinelli, E.; Paliani, U.; Cesari, E.; Vaudo, G.; Sebastiano, M.; Cerotto, V.; Guglielmini, G.; Gori, F.; Malvestiti, M.; et al. Association of Neutrophil Activation, More Than Platelet Activation, With Thrombotic Complications in Coronavirus Disease 2019. *J. Infect. Dis.* **2021**, *223*, 933–944. [[CrossRef](#)]
83. Shaw, R.J.; Abrams, S.T.; Austin, J.; Taylor, J.M.; Lane, S.; Dutt, T.; Downey, C.; Du, M.; Turtle, L.; Baillie, J.K.; et al. Circulating histones play a central role in COVID-19-associated coagulopathy and mortality. *Haematologica* **2021**. Epub ahead of print. [[CrossRef](#)] [[PubMed](#)]
84. Bye, A.P.; Hoepel, W.; Mitchell, J.L.; Jégouic, S.M.; Loureiro, S.; Sage, T.; Vidarsson, G.; Nouta, J.; Wührer, M.; de Taeye, S.W.; et al. Aberrant glycosylation of anti-SARS-CoV-2 IgG is a pro-thrombotic stimulus for platelets. *Blood* **2021**. [[CrossRef](#)] [[PubMed](#)]
85. Brodard, J.; Kremer Hovinga, J.A.; Fontana, P.; Studt, J.D.; Gruel, Y.; Greinacher, A. COVID-19 patients often show high-titer non-platelet-activating anti-PF4/heparin IgG antibodies. *J. Thromb. Haemost.* **2021**, *19*, 1294–1298. [[CrossRef](#)] [[PubMed](#)]

86. Zuo, Y.; Estes, S.K.; Ali, R.A.; Gandhi, A.A.; Yalavarthi, S.; Shi, H.; Sule, G.; Gockman, K.; Madison, J.A.; Zuo, M.; et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. *Sci. Transl. Med.* **2020**, *12*, eabd3876. [[CrossRef](#)] [[PubMed](#)]
87. Henderson, L.A.; Canna, S.W.; Schulert, G.S.; Volpi, S.; Lee, P.Y.; Kernan, K.F.; Caricchio, R.; Mahmud, S.; Hazen, M.M.; Halyabar, O.; et al. On the Alert for Cytokine Storm: Immunopathology in COVID-19. *Arthritis Rheumatol.* **2020**, *72*, 1059–1063. [[CrossRef](#)] [[PubMed](#)]
88. Blanco-Melo, D.; Nilsson-Payant, B.E.; Liu, W.C.; Uhl, S.; Hoagland, D.; Möller, R.; Jordan, T.X.; Oishi, K.; Panis, M.; Sachs, D.; et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. *Cell* **2020**, *181*, 1036–1045. [[CrossRef](#)]
89. Vanderheiden, A.; Ralfs, P.; Chirkova, T.; Upadhyay, A.A.; Zimmerman, M.G.; Bedoya, S.; Aoued, H.; Tharp, G.M.; Pellegrini, K.L.; Manfredi, C.; et al. Type I and Type III Interferons Restrict SARS-CoV-2 Infection of Human Airway Epithelial Cultures. *J. Virol.* **2020**, *94*, e0098520. [[CrossRef](#)]
90. Zheng, Y.; Zhuang, M.W.; Han, L.; Zhang, J.; Nan, M.L.; Zhan, P.; Kang, D.; Liu, X.; Gao, C.; Wang, P.H. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) membrane (M) protein inhibits type I and III interferon production by targeting RIG-I/MDA-5 signaling. *Signal. Transduct. Target. Ther.* **2020**, *5*, 299. [[CrossRef](#)]
91. Burgos-Blasco, B.; Güemes-Villahoz, N.; Santiago, J.L.; Fernandez-Vigo, J.I.; Espino-Paisán, L.; Sarriá, B.; García-Feijoo, J.; Martínez-de-la-Casa, J.M. Hypercytokinemia in COVID-19: Tear cytokine profile in hospitalized COVID-19 patients. *Exp. Eye Res.* **2020**, *200*, 108253. [[CrossRef](#)]
92. Sang, Y.; Miller, L.C.; Blecha, F. Macrophage Polarization in Virus-Host Interactions. *J. Clin. Cell Immunol.* **2015**, *6*, 311.
93. Mahajan, S.; Decker, C.E.; Yang, Z.; Veis, D.; Mellins, E.D.; Faccio, R. Plcγ2/Tmem178 dependent pathway in myeloid cells modulates the pathogenesis of cytokine storm syndrome. *J. Autoimmun.* **2019**, *100*, 62–74. [[CrossRef](#)]
94. Holter, J.C.; Pischke, S.E.; de Boer, E.; Lind, A.; Jennum, S.; Holten, A.R.; Tonby, K.; Barratt-Due, A.; Sokolova, M.; Schjalm, C.; et al. Systemic complement activation is associated with respiratory failure in COVID-19 hospitalized patients. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 25018–25025. [[CrossRef](#)] [[PubMed](#)]
95. Soy, M.; Keser, G.; Atagündüz, P.; Tabak, F.; Atagündüz, I.; Kayhan, S. Cytokine storm in COVID-19: Pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin. Rheumatol.* **2020**, *39*, 2085–2094. [[CrossRef](#)] [[PubMed](#)]
96. Hussman, J.P. Severe Clinical Worsening in COVID-19 and Potential Mechanisms of Immune-Enhanced Disease. *Front. Med.* **2021**, *8*, 637642. [[CrossRef](#)] [[PubMed](#)]
97. Cardone, M.; Yano, M.; Rosenberg, A.S.; Puig, M. Lessons Learned to Date on COVID-19 Hyperinflammatory Syndrome: Considerations for Interventions to Mitigate SARS-CoV-2 Viral Infection and Detrimental Hyperinflammation. *Front. Immunol.* **2020**, *11*, 1131. [[CrossRef](#)] [[PubMed](#)]
98. Kaur, S.; Bansal, R.; Kollimuttathuillam, S.; Gowda, A.M.; Singh, B.; Mehta, D.; Maroules, M. The looming storm: Blood and cytokines in COVID-19. *Blood Rev.* **2020**, *46*, 100743. [[CrossRef](#)] [[PubMed](#)]
99. Quartuccio, L.; Sonaglia, A.; McGonagle, D.; Fabris, M.; Peghin, M.; Pecori, D.; De Monte, A.; Bove, T.; Curcio, F.; Bassi, F.; et al. Profiling COVID-19 pneumonia progressing into the cytokine storm syndrome: Results from a single Italian Centre study on tocilizumab versus standard of care. *J. Clin. Virol.* **2020**, *129*, 104444. [[CrossRef](#)] [[PubMed](#)]
100. Didangelos, A. COVID-19 Hyperinflammation: What about Neutrophils? *mSphere* **2020**, *5*, e00367. [[CrossRef](#)]
101. Mokhtari, T.; Hassani, F.; Ghaffari, N.; Ebrahimi, B.; Yarahmadi, A.; Hassanzadeh, G. COVID-19 and multiorgan failure: A narrative review on potential mechanisms. *J. Mol. Histol.* **2020**, *51*, 613–628. [[CrossRef](#)]
102. Kim, J.S.; Lee, J.Y.; Yang, J.W.; Lee, K.H.; Effenberger, M.; Szpirt, W.; Kronbichler, A.; Shin, J.I. Immunopathogenesis and treatment of cytokine storm in COVID-19. *Theranostics* **2021**, *11*, 316–329. [[CrossRef](#)]
103. Monteagudo, L.A.; Boothby, A.; Gertner, E. Continuous Intravenous Anakinra Infusion to Calm the Cytokine Storm in Macrophage Activation Syndrome. *ACR Open Rheumatol.* **2020**, *2*, 276–282. [[CrossRef](#)]
104. Ucciferri, C.; Auricchio, A.; Di Nicola, M.; Potere, N.; Abbate, A.; Cipollone, F.; Vecchiet, J.; Falasca, K. Canakinumab in a subgroup of patients with COVID-19. *Lancet Rheumatol.* **2020**, *2*, e457–e458. [[CrossRef](#)]
105. Kalil, A.C.; Patterson, T.F.; Mehta, A.K.; Tomashek, K.M.; Wolfe, C.R.; Ghazaryan, V.; Marconi, V.C.; Ruiz-Palacios, G.M.; Hsieh, L.; Kline, S.; et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N. Engl. J. Med.* **2021**, *384*, 795–807. [[CrossRef](#)] [[PubMed](#)]
106. Kaplanski, G.; Bontemps, D.; Esnault, P.; Blasco, V.; Carvelli, J.; Delarbre, D.; Cauchois, R.; Forel, J.M.; Papazian, L. Combined Anakinra and Ruxolitinib treatment to rescue extremely ill COVID-19 patients: A pilot study. *Autoimmun. Rev.* **2021**, *20*, 102726. [[CrossRef](#)] [[PubMed](#)]
107. Salama, C.; Han, J.; Yau, L.; Reiss, W.G.; Kramer, B.; Neidhart, J.D.; Criner, G.J.; Kaplan-Lewis, E.; Baden, R.; Pandit, L.; et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N. Engl. J. Med.* **2021**, *384*, 20–30. [[CrossRef](#)]
108. Leaf, D.E.; Gupta, S.; Wang, W. Tocilizumab in Covid-19. *N. Engl. J. Med.* **2021**, *384*, 86–87.
109. Emadi, A.; Chua, J.V.; Talwani, R.; Bentzen, S.M.; Baddley, J. Safety and Efficacy of Imatinib for Hospitalized Adults with COVID-19: A structured summary of a study protocol for a randomised controlled trial. *Trials* **2020**, *21*, 897. [[CrossRef](#)]
110. Petrova, M.; Jelev, D.; Ivanova, A.; Krastev, Z. Isoprinosine affects serum cytokine levels in healthy adults. *J. Interf. Cytokine Res.* **2010**, *30*, 223–228. [[CrossRef](#)]
111. Lasek, W.; Janyst, M.; Wolny, R.; Zapala, L.; Bocian, K.; Drela, N. Immunomodulatory effects of inosine pranobex on cytokine production by human lymphocytes. *Acta Pharm.* **2015**, *65*, 171–180. [[CrossRef](#)]

112. Beran, J.; Špajdel, M.; Katzerová, V.; Holoušová, A.; Malyš, J.; Finger-Rousková, J.; Slíva, J. Inosine Pranobex Significantly Decreased the Case-Fatality Rate among PCR Positive Elderly with SARS-CoV-2 at Three Nursing Homes in the Czech Republic. *Pathogens* **2020**, *9*, 1055. [[CrossRef](#)]
113. Wu, L.; Davies, G.J. An Overview of the Structure, Mechanism and Specificity of Human Heparanase. *Adv. Exp. Med. Biol.* **2020**, *1221*, 139–167.
114. Nadir, Y.; Brenner, B.; Fux, L.; Shafat, I.; Attias, J.; Vlodaysky, I. Heparanase enhances the generation of activated factor X in the presence of tissue factor and activated factor VII. *Haematologica* **2010**, *95*, 1927–1934. [[CrossRef](#)]
115. Cui, H.; Tan, Y.X.; Österholm, C.; Zhang, X.; Hedin, U.; Vlodaysky, I.; Li, J.P. Heparanase expression upregulates platelet adhesion activity and thrombogenicity. *Oncotarget* **2016**, *7*, 39486–39496. [[CrossRef](#)]
116. Buijssers, B.; Yanginlar, C.; de Nooijer, A.; Grondman, I.; Maciej-Hulme, M.L.; Jonkman, I.; Janssen, N.A.F.; Rother, N.; de Graaf, M.; Pickkers, P.; et al. Increased Plasma Heparanase Activity in COVID-19 Patients. *Front. Immunol.* **2020**, *11*, 575047. [[CrossRef](#)]
117. Paar, V.; Wernly, B.; Zhou, Z.; Motloch, L.J.; Hoppe, U.C.; Egle, A.; Lichtenauer, M. Anti-coagulation for COVID-19 treatment: Both anti-thrombotic and anti-inflammatory? *J. Thromb. Thrombolysis* **2021**, *51*, 226–231. [[CrossRef](#)] [[PubMed](#)]
118. Buijssers, B.; Yanginlar, C.; Maciej-Hulme, M.L.; de Mast, Q.; van der Vlag, J. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. *EBioMedicine* **2020**, *59*, 102969. [[CrossRef](#)] [[PubMed](#)]
119. Garcia, D.A.; Baglin, T.P.; Weitz, J.I.; Samama, M.M. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* **2013**, *141* (Suppl. 2), e24S–e43S, Erratum in **2013**, *144*, 721.
120. Longstaff, C.; Hogwood, J.; Gray, E.; Komorowicz, E.; Varjú, I.; Varga, Z.; Kolev, K. Neutralisation of the anti-coagulant effects of heparin by histones in blood plasma and purified systems. *Thromb. Haemost.* **2016**, *115*, 591–599. [[PubMed](#)]
121. Kilgore, K.S.; Tanhehco, E.J.; Naylor, K.B.; Lucchesi, B.R. Ex vivo reversal of heparin-mediated cardioprotection by heparinase after ischemia and reperfusion. *J. Pharm. Exp. Ther.* **1999**, *290*, 1041–1047.
122. Hippensteel, J.A.; LaRiviere, W.B.; Colbert, J.F.; Langouët-Astrié, C.J.; Schmidt, E.P. Heparin as a therapy for COVID-19: Current evidence and future possibilities. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2020**, *319*, L211–L217. [[CrossRef](#)]
123. Stattin, K.; Lipcsey, M.; Andersson, H.; Pontén, E.; Bülow Anderberg, S.; Gradin, A.; Larsson, A.; Lubenow, N.; von Seth, M.; Rubertsson, S.; et al. Inadequate prophylactic effect of low-molecular weight heparin in critically ill COVID-19 patients. *J. Crit. Care* **2020**, *60*, 249–252. [[CrossRef](#)] [[PubMed](#)]
124. Capell, W.H.; Barnathan, E.S.; Piazza, G.; Spyropoulos, A.C.; Hsia, J.; Bull, S.; Lipardi, C.; Sugarmann, C.; Suh, E.; Rao, J.P.; et al. Rationale and design for the study of rivaroxaban to reduce thrombotic events, hospitalization and death in outpatients with COVID-19: The PREVENT-HD study. *Am. Heart J.* **2021**, *235*, 12–23. [[CrossRef](#)]
125. Akel, T.; Qaqa, F.; Abuarqoub, A.; Shamoon, F. Pulmonary embolism: A complication of COVID 19 infection. *Thromb. Res.* **2020**, *193*, 79–82. [[CrossRef](#)]
126. Gots, J.E.; Matthay, M.A. Sepsis: Pathophysiology and clinical management. *BMJ* **2016**, *353*, i1585. [[CrossRef](#)]
127. Taeb, A.M.; Hooper, M.H.; Marik, P.E. Sepsis: Current Definition, Pathophysiology, Diagnosis, and Management. *Nutr. Clin. Pract.* **2017**, *32*, 296–308. [[CrossRef](#)] [[PubMed](#)]
128. Clausen, T.M.; Sandoval, D.R.; Spliid, C.B.; Pihl, J.; Perrett, H.R.; Painter, C.D.; Narayanan, A.; Majowicz, S.A.; Kwong, E.M.; McVicar, R.N.; et al. SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. *Cell* **2020**, *183*, 1043–1057. [[CrossRef](#)]
129. Mycroft-West, C.J.; Su, D.; Pagani, I.; Rudd, T.R.; Elli, S.; Gandhi, N.S.; Guimond, S.E.; Miller, G.J.; Meneghetti, M.C.Z.; Nader, H.B.; et al. Heparin Inhibits Cellular Invasion by SARS-CoV-2: Structural Dependence of the Interaction of the Spike S1 Receptor-Binding Domain with Heparin. *Thromb. Haemost.* **2020**, *120*, 1700–1715. [[PubMed](#)]
130. Nandy, A.; Mondal, T.; Sarkar, M.; Nag, S.S.; Chel, S.; Ivan, D.M.; Hazra, A.; Mondal, R. Multiorgan dysfunction syndrome in sepsis: Is macrophage activation syndrome secondary to infection? *Eur. J. Rheumatol.* **2020**, *8*, 89–92. [[CrossRef](#)] [[PubMed](#)]
131. Marsman, G.; von Richthofen, H.; Bulder, I.; Lupu, F.; Hazelzet, J.; Luken, B.M.; Zeerleder, S. DNA and factor VII-activating protease protect against the cytotoxicity of histones. *Blood Adv.* **2017**, *1*, 2491–2502. [[CrossRef](#)]
132. Yamamichi, S.; Fujiwara, Y.; Kikuchi, T.; Nishitani, M.; Matsushita, Y.; Hasumi, K. Extracellular histone induces plasma hyaluronan-binding protein (factor VII activating protease) activation in vivo. *Biochem. Biophys. Res. Commun.* **2011**, *409*, 483–488. [[CrossRef](#)]
133. Cosmi, B.; Cini, M.; Legnani, C.; Pancani, C.; Calanni, F.; Coccheri, S. Additive thrombin inhibition by fast moving heparin and dermatan sulfate explains the anticoagulant effect of sulodexide, a natural mixture of glycosaminoglycans. *Thromb. Res.* **2003**, *109*, 333–339. [[CrossRef](#)]
134. Siddiqui, F.; Hoppensteadt, D.; Bontekoe, E.; Farooqui, A.; Jeske, W.; Fareed, J. Comparative Anticoagulant and Thrombin Generation Inhibitory Profile of Heparin, Sulodexide and Its Components. *Clin. Appl. Thromb. Hemost.* **2020**, *26*, 1076029620954913. [[CrossRef](#)] [[PubMed](#)]
135. De Felice, F.; Megiorni, F.; Pietrantonio, I.; Tini, P.; Lessiani, G.; Mastroiacovo, D.; Mattana, P.; Antinozzi, C.; Di Luigi, L.; Delle Monache, S.; et al. Sulodexide counteracts endothelial dysfunction induced by metabolic or non-metabolic stresses through activation of the autophagic program. *Eur. Rev. Med. Pharm. Sci.* **2019**, *23*, 2669–2680.
136. Borawski, J.; Gozdzikiewicz, J.; Dubowski, M.; Pawlak, K.; Mysliwiec, M. Tissue factor pathway inhibitor release and depletion by sulodexide in humans. *Adv. Med. Sci.* **2009**, *54*, 32–36. [[CrossRef](#)] [[PubMed](#)]

137. White, D.; MacDonald, S.; Edwards, T.; Bridgeman, C.; Hayman, M.; Sharp, M.; Cox-Morton, S.; Duff, E.; Mahajan, S.; Moore, C.; et al. Evaluation of COVID-19 coagulopathy; laboratory characterization using thrombin generation and nonconventional haemostasis assays. *Int. J. Lab. Hematol.* **2021**, *43*, 123–130. [[CrossRef](#)]
138. Daly, J.L.; Simonetti, B.; Klein, K.; Chen, K.E.; Williamson, M.K.; Antón-Plágaro, C.; Shoemark, D.K.; Simón-Gracia, L.; Bauer, M.; Hollandi, R.; et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. *Science* **2020**, *370*, 861–865. [[CrossRef](#)]
139. Liaw, P.C.; Becker, D.L.; Stafford, A.R.; Fredenburgh, J.C.; Weitz, J.I. Molecular basis for the susceptibility of fibrin-bound thrombin to inactivation by heparin cofactor ii in the presence of dermatan sulfate but not heparin. *J. Biol. Chem.* **2001**, *276*, 20959–20965. [[CrossRef](#)]