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Endothelial dysfunction and thrombotic complications associated with SARS-CoV-2 in adults: a systematic review

Disfunção endotelial e complicações trombóticas associada a SARS-CoV-2 em adultos: uma revisão sistemática

Disfunción endotelial y complicaciones trombóticas asociadas al SARS-CoV-2 en adultos: una revisión sistemática

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Abstract
Introduction: During the pandemic, occurrences of thromboembolic complications and endothelial dysfunctions associated with COVID-19 were observed. Thus, the pathophysiology of the mechanisms of action are not fully elucidated. Methods: Aiming at a better understanding of the associated mechanisms of endothelial function due to COVID-19, a systematic review was developeded out using index databases and a selection process in which the inclusion criteria were articles that addressed the mechanism of thrombotic events by endothelium dysfunction and publications that associate COVID-19 with thrombotic complications in adults up to 59 years of age. Conclusion: SARS-CoV-2 is associated with altered endothelial function by endothelial mechanisms induced by direct viral infection and injury, leading to changes in the angiotensin II/AT1 axis and inflammatory response.
Keywords: SARS-CoV-2; Adult; Endothelial dysfunction; Thrombotic complications.

Resumo
Introdução: Durante a pandemia, foram constatadas ocorrências de complicações tromboembólicas e disfunções endoteliais associadas ao COVID-19. Entretanto, a fisiopatologia dos mecanismos de ação não estão totalmente elucidados. Métodos: visando melhor entendimento dos mecanismos associados da função endotelial devido ao COVID-19 foi realizada uma revisão sistemática desenvolvida por meio de bases de dados de indexadores e processo de seleção no qual os critérios de inclusão foram artigos que abordassem o mecanismo dos eventos trombóticos por meio da disfunção do endotélio e publicações que associam a COVID-19 as complicações trombóticas em adultos até

59 anos. Conclusão: a SARS-CoV-2 está associada a alteração função endotelial por mecanismos endoteliais induzida por infecção viral direta e por lesão, levando a mudanças no eixo angiotensina II/AT1 e resposta inflamatória.
Palavras-chave: SARS-CoV-2; Adulto; Disfunção endotelial; Complicações trombóticas.

Resumen
Introducción: Durante la pandemia se observaron ocurrencias de complicaciones tromboembólicas y disfunciones endoteliales asociadas a la COVID-19. Sin embargo, la fisiopatología de los mecanismos de acción no está completamente dilucidada. Métodos: Con el objetivo de una mejor comprensión de los mecanismos asociados de la función endotelial debido a COVID-19, se realizó una revisión sistemática utilizando bases de datos índice y un proceso de selección en el que los criterios de inclusión fueron artículos que abordan el mecanismo de eventos trombóticos por disfunción endotelial. y publicaciones que asocian COVID-19 con complicaciones trombóticas en adultos de hasta 59 años. Conclusión: el SARS-CoV-2 está asociado con una función endotelial alterada por mecanismos endoteliales inducidos por infección y lesión viral directa, lo que lleva a cambios en el eje angiotensina II/AT1 y respuesta inflamatoria.
Palabras clave: SARS-CoV-2; Adulto; Disfunción endotelial; Complicaciones trombóticas.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome (SARS) caused by the SARS-CoV-2 coronavirus that has reached pandemic proportions since December 2019, with more than 3 million confirmed cases worldwide and more than 260,000 deaths in just 5 months (Róman et al., 2020).

This way, when being notified of the hypothesis of the outbreak in Wuhan, China, having been caused by a new strain of the coronavirus, the World Health Organization (WHO) declared a public health emergency of international concern (WHO, 2020).

All systemic manifestations of COVID-19, including thrombotic complications, are considered to be caused by direct endothelial dysfunction in infected patients, as human endothelial cells express ACE2, CD147, sialic acid receptor and transmembrane serine protease 2. Cofactors linked by the COVID-19 virus to access host cells. In addition, the risk of a large-vessel and cardiogenic cerebrovascular accident (CVA) has already been described in the literature, even without the classic factors for this in individuals with an infected respiratory tract (Amoah et al., 2020).

Angiotensin converting enzyme 2 (ACE2) combines with the spike surface protein of host cells when SARS-CoV-2 invades them. This enzyme is widely expressed in arterial and venous endothelial cells, epithelial cells, neurocortex, brainstem, neural cortex, alveolar cells, muscle cells of organs and enterocytes of the small intestine. (Fei et al., 2020).

So much that it is believed that diffuse endotheliitis is caused by endothelial damage arising from this mechanism between ACE2 and SARS-CoV-2, as damage to endothelial cells can lead to excessive host immune activation, thrombosis and a procoagulant/hypercoagulable state that eventually evolves for diffuse intravascular coagulation, leading to embolism and multi-organ failure. In addition, microvascular thrombosis occurs systematically and can also affect various organs (Chen & Pan, 2021).

2. Methodology

This is a systematic review with a protocol registered at OSF (https://osf.io/r425d). Inclusion criteria were articles that addressed the mechanism of thrombotic events through endothelial dysfunction and publications that associated COVID-19 with thrombotic complications in adults up to 59 years of age. There was no restriction on date of publication or language.

Search strategy

At first, the gathering of the published literature took place between August 1, 2021 and June 25, 2022, aiming at understanding the subject for the elaboration of the project. To identify the published literature, individual search strategies were

applied in the following databases: PubMed, Cinahl, Web of Science and Embase using DeCS/MeSH descriptors and Boolean operators. (Table 1)

Table 1 - Search Strategy.

DATA BASE	STRATEGY	RESULT
Pubmed	("adult"[All Fields] OR "adults"[All Fields] OR "young adult"[All Fields] OR "young adults"[All Fields]) AND ("COVID-19"[All Fields] OR "2019 novel coronavirus disease"[All Fields] OR "COVID19"[All Fields] OR "SARS-CoV-2 infection"[All Fields] OR "COVID-19 virus disease"[All Fields] OR "coronavirus disease 2019"[All Fields] OR "coronavirus disease-19"[All Fields] OR "COVID-19 virus infection"[All Fields] OR "ômicron" [All Fields]"sars-cov-2"[All Fields]) AND ("endothelium"[All Fields] OR "Endothelial Cell"[All Fields] OR "Endothelial Cells"[All Fields] OR "cell endothelial"[All Fields] OR "cells endothelial"[All Fields] OR "Vascular Endothelial Cell"[All Fields] OR "Vascular Endothelial Cells"[All Fields] OR "cell vascular endothelial"[All Fields] OR "cells vascular endothelial"[All Fields] OR "endothelial cell vascular"[All Fields] OR "endothelial cells vascular"[All Fields] OR "ACE2 Protein"[All Fields] OR "ACE2 Receptors"[All Fields]) AND ("Stroke"[All Fields] OR "Strokes"[All Fields] OR "Ischemic Stroke"[All Fields] OR "Ischemic Strokes"[All Fields] OR "Thrombosis"[All Fields] OR "Thromboses"[All Fields] OR "Venous Thrombosis"[All Fields] OR "Venous Thromboses"[All Fields] OR "Intracranial Thrombosis"[All Fields] OR "Intracranial Thromboses"[All Fields] OR "Endotheliitis"[All Fields] OR "Cerebral Venous Thrombosis"[All Fields] OR "Cerebral Venous Thromboses"[All Fields])	53
Web of Science	TS=("adult" OR "adults" OR "young adult" OR "young adults") AND TS=("COVID-19" OR "2019 novel coronavirus disease" OR "COVID19" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "coronavirus disease 2019" OR "ômicron" OR "coronavirus disease-19" OR "COVID-19 virus infection" OR "sars-cov-2" OR "endothelium" OR "Endothelial Cell" OS "Endothelial Cells" OR "Cell, Endothelial" OR "Cells, Endothelial" OR "Vascular Endothelial Cell" OR "Vascular Endothelial Cells" OR "Cell, Vascular Endothelial" OR "Cells, Vascular Endothelial" OR "Endothelial Cell, Vascular" OR "Endothelial Cells, Vascular" OR "ACE2 Protein" OR "ACE2 Receptors") AND TS=("stroke" OR "strokes" OR "Ischemic Stroke" OR "Ischemic Strokes" OR "Thrombosis" OR "Thromboses" OR "Venous Thrombosis" OR "Venous Thromboses" OR "Intracranial Thrombosis" OR "Intracranial Thromboses" OR "Endotheliitis" OR "Cerebral Venous Thrombosis" OR "Cerebral Venous Thromboses")	537
Embase	('adult' OR 'adults' OR 'young adult' OR 'young adults') AND ('covid 19' OR '2019 novel coronavirus disease' OR 'covid19' OR 'sars cov 2 infection' OR 'covid-19 virus disease' OR 'coronavirus disease2019' OR 'coronavirus disease-19' OR 'covid-19 virus infection' OR 'sars cov 2') OR 'ômicron' AND ('endothelium' OR 'endothelial cell' OR 'endothelial cells' OR 'cell, endothelial' OR 'cells, endothelial' OR 'vascular endothelial cell' OR 'vascular endothelial cells' OR 'cell, vascular endothelial' OR 'cells, vascular endothelial' OR 'endothelial cell, vascular' OR 'endothelial cells, vascular' OR 'ace2 protein' OR 'ace2 receptors') AND ('stroke' OR 'strokes' OR 'ischemic stroke' OR 'ischemic strokes' OR 'thrombosis' OR 'thromboses' OR 'venous thrombosis' OR 'venous thromboses' OR 'intracranial thrombosis' OR 'intracranial thromboses' OR 'endotheliitis' OR 'cerebral venous thrombosis' OR 'cerebral venous thromboses')	500
CINAHL	("adult" OR "adults" OR "young adult" OR "young adults") AND ("COVID-19" OR "2019 novel coronavirus disease" OR "COVID19" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "COVID-19 virus infection" OR "sars-cov-2") AND ("endothelium" OR "Endothelial Cell" OS "Endothelial Cells" OR "Cell, Endothelial" OR "Cells, Endothelial" OR "Vascular Endothelial Cell" OR "Vascular Endothelial Cells" OR "Cell, Vascular Endothelial" OR "Cells, Vascular Endothelial" OR "Endothelial Cell, Vascular" OR "Endothelial Cells, Vascular" OR "ACE2 Protein" OR "ACE2 Receptors") AND ("stroke" OR "strokes" OR "Ischemic Stroke" OR "Ischemic Strokes" OR "Thrombosis" OR "Thromboses" OR "Venous Thrombosis" OR "Venous Thromboses" OR "Intracranial Thrombosis" OR "Intracranial Thromboses" OR "Endotheliitis" OR "Cerebral Venous Thrombosis" OR "Cerebral Venous Thromboses")	34

Source: Pamplona (2022).

Study selection process

The studies collected from the indexers were entered into Mendeley Desktop. From then on, the selection was carried out manually by two independent evaluators, divided into three stages: 1. Pre-analysis: verification of texts through title and abstract in order to verify their eligibility based on the criteria described in the methodology; 2. Exploration of the material: the articles were selected based on their ability to answer the research question; 3. Treatment of the results: critical analysis of the articles selected for the conclusion of this study.

Data extraction and synthesis

After selecting the articles used for the study, data such as: name of the main author; purpose of the study; kind of study; outcome; Thrombotic complications and complications after endothelial dysfunction were entered manually into a table generated by the Microsoft Word 2016© program (Table 2).

Table 2 - Bibliographic search results table.

AUTHOR/YEAR	OBJECTIVE	LEVEL OF EVIDENCE	OUTCOME
Almyroudi & Dimopoulos (2020)	To evaluate thromboembolic complications in critically ill patients with COVID-19.	Cohort study	The hyperinflammatory state in combination with endothelial damage by the virus and diffuse microvascular thrombosis contribute to the pathogenesis.
Canzano et al. (2020)	To evaluate platelet and endothelial activation in 46 patients infected with SARS-CoV-2	Cohort study	It suggests a close relationship between IL-6 and the triggering of hypercoagulability secondary to COVID-19.
Carmeliet (2021)	To research the viral relationship of SARS-CoV-2 with endothelial cells and inflammatory changes.	Cohort study	Emerging evidence suggests that the virus alters vessel barrier integrity, promoting a procoagulative state, inducing inflammation (endothelitis) and mediating inflammatory cell infiltration.
Freda et al. (2021)	To investigate how the pro-thrombotic and pro-inflammatory responses of endothelial cells are altered after exposure to the spike, nucleocap-sid and membrane-envelope proteins of SARS-CoV-2.	Cohort study	Significant increases in the expression of thrombotic and inflammatory markers were found, with no change in cell culture parameters.
Gencer et al. (2020)	To examine mechanisms that may explain how viral entry and endothelial cell activation by SARS-CoV-2 can give rise to systemic inflammation, thrombosis and microvascular dysfunction.	Cohort study	Recognizing comorbidities and potential organ damage over the course of severe COVID-19 is crucial in the clinical management of patients that affect treatment approaches and recovery rate.
Agrati et al. (2021)	The objective of the study was to investigate, in critically ill patients hospitalized with COVID-19, the plasma concentration of P-selectin as a biomarker of endothelial dysfunction and platelet activation.	Case-control study	Elevated P-selectin suggests a central role for platelet endothelial interaction as part of the multifaceted pathogenic mechanism of COVID-19, leading to local activation of the hemostatic system forming pulmonary thrombi.
Nagashima et al. (2020)	To identify tissue biomarkers associated with endothelial activation/dysfunction and the pyroptosis pathway in lung samples from patients with COVID-19.	Case-control study	The results demonstrated endothelial dysfunction and suggested the participation of the pyroptosis pathway in lung samples.
Schmaier et al. (2021)	To assess whether severe COVID-19 is associated with procoagulant endothelial dysfunction and changes in the Tie2/angiopoietin axis.	Cohort study	In conclusion, by the dysfunction of procoagulant endothelial cells, the degree of which increases in parallel with the severity of the COVID-19 disease. Elevated levels of Angpt-2 may potentiate

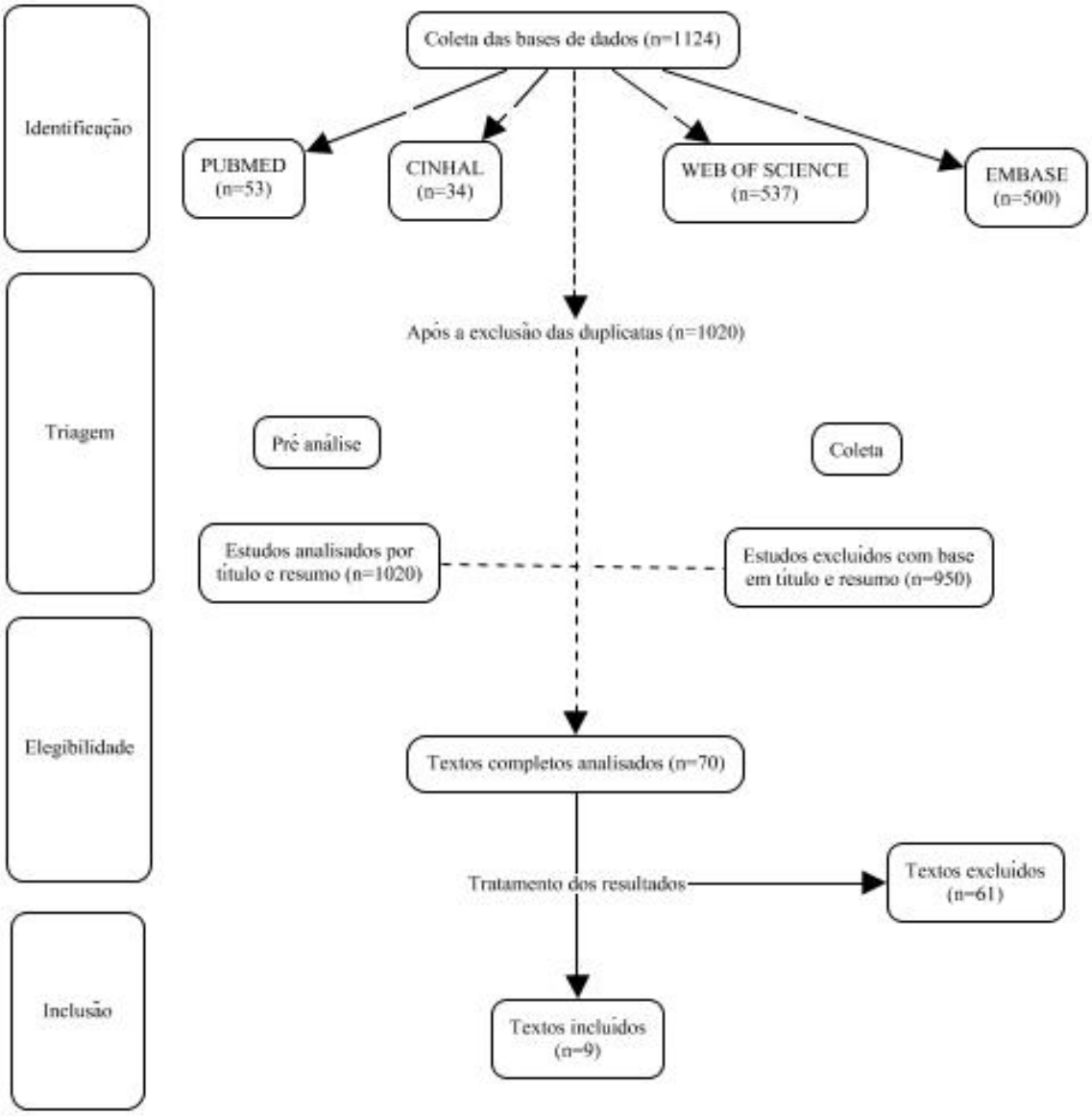
			endothelial cell dysfunction through inhibition of Tie2 antithrombotic signaling.
Zhang et al, (2020)	To assess platelet and coagulation changes in patients with COVID-19.	Case-control study	SARS-CoV-2-induced platelet activation may participate in thrombus formation and inflammatory responses in patients with COVID-19.

Source: Pamplona (2022).

3. Results and Discussion

At the end of the searches, 1124 articles were collected, of which 104 were duplicates. During the pre-analysis phase 1020 were evaluated and 950 excluded as reported in the study selection process based on title and abstract. During the period of exploration of the material, 61 studies out of 70 were excluded because they did not answer the main question of the research. The flowchart of the results built according to the PRISMA method, which can be viewed as shown in Figure 1.

Figure 1 - PRISMA study selection and inclusion process flowchart.



Source: Pamplona (2022).

Nine original studies were selected to further analyze the possible endothelial and thrombotic effects of COVID-19. In a deeper inspection, it was possible to observe the exams used to investigate possible complications. Among the exams, PCR was performed in 3/9 (33.32%) of the articles. Other tests that were also evidenced are: D-dimer dosage – D-dimer, Activated Partial Thromboplastin Time – APTT in 33.32% of the cases. Research for Deep Vein Thrombosis – DVT by means of ultrasound corresponds only to 2/9 (22.21%). However, the Prothrombin Test - PT occurred in 4/9 which corresponds to 44.43% of the results, which together with APTT evaluates the coagulation capacity.

Among the cases of thromboembolism identified in the study (9/9), complications could also be evidenced, such as venous thromboembolism and hypoxia that occurred in 5/9 (55.56%) of the cases, followed by Disseminated Intravascular Coagulation - DIC that corresponds to 44.43% of the cases and DVT which was evidenced in 33.32%. The results can also be analyzed in Table 3.

Table 3 - Thrombotic Complications.

A. Post-thrombotic complication	Sample result	B. Exams	Sample result
Hypoxia	5/9	PCR	3/9
TVP	3/9	D-dimer	3/9
TEV	5/9	TPA	3/9
CID	4/9	TP	4/9
		Ultrasound	2/9

Source: Pamplona (2022).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes injury to pneumocytes and contributes to the release of inflammatory cytokines that subsequently damage the endothelium. Furthermore, endothelial cells express ACE-2 (angiotensin-converting enzyme) which is associated with SARS-CoV-2 infection (Nagashima et. al., 2020). Excessive production of oxidative stress is triggered by functional ACE-2. Thus, it induces TNF-α and stimulates NADPH-oxidase in serial clinical examination, further regulating the expression of endothelial adhesion molecules, such as ICAM-1, and increasing cell permeability (Ma et al., 2022).

A cohort of lung autopsy samples from 98 patients with mild, moderate, or severe COVID-19 was assessed using circulating endothelial markers and revealed deep endothelial dysfunction indicative of a prothrombotic state. In addition, a prothrombotic endothelial signature was found, evidenced by an increase in Von Willebrand factor and loss of anticoagulant proteins (Schamaier et. al., 2021).

Anticoagulant and antiplatelet molecules are observed in the endothelial cell. This is covered by a glycocalyx that serves as a barrier against platelets and blood cells. Compromise of the glycocalyx would lead to endothelial activation, endothelitis and thrombotic events (endotheliopathy or endothelial dysfunction) (Nagashima et al., 2020).

Under prothrombotic conditions, capillary-alveolar endothelial cells receive a shower of cytokines from infected SARS-CoV-2 pneumocytes, and breakdown of the glycocalyx promotes endothelial dysfunction and thrombosis. In part, the higher levels of IL-6 and TNF-α in the COVID-19 group are responsible for the endothelial dysfunction (Nagashima et al., 2020).

Furthermore, endothelial cells contribute to the onset and spread of acute respiratory distress syndrome (ARDS), according to emerging evidence, by altering the integrity of the vascular barrier, inducing vascular inflammation (endothelitis), promoting a procoagulative state, and mediating the inflammatory cell infiltration (Carmeliet, 2021).

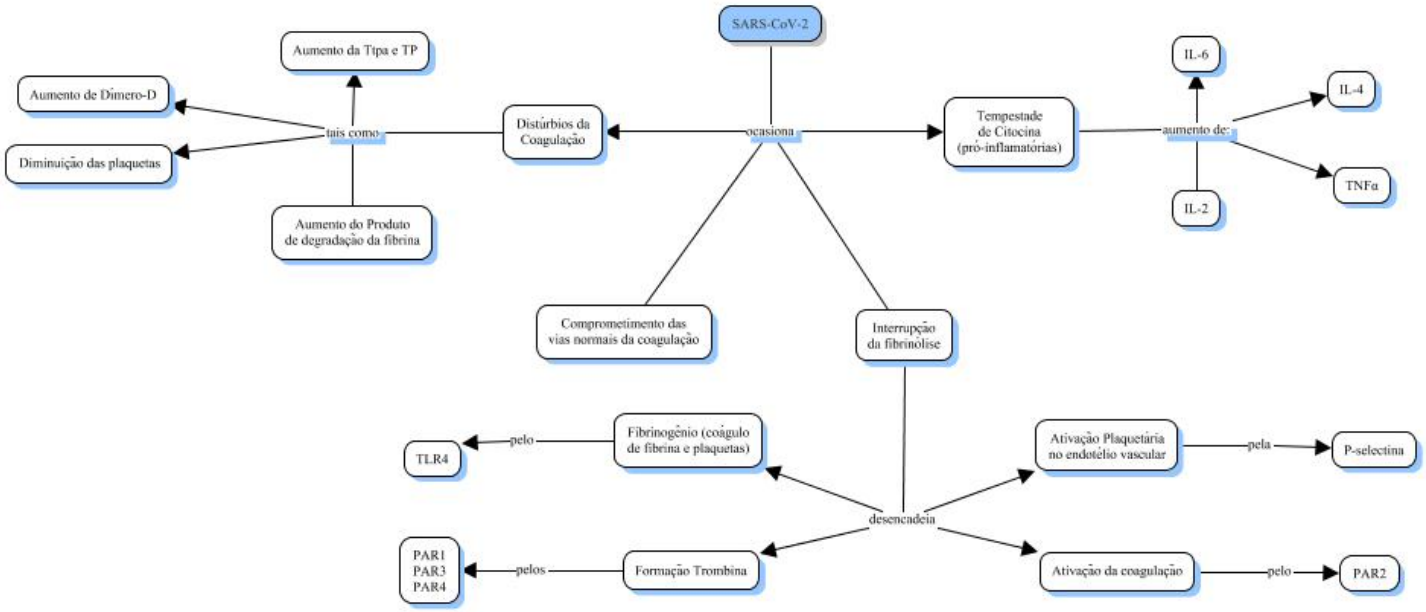
The protein angiotensin converting enzyme 2 (ACE2) is a central regulator of the renin-angiotensin aldosterone system (RAAS), a hormonal system that influences the maintenance of blood pressure and fluids. Imbalance can lead to increased inflammation and thrombosis. ACE2 is used by SARS CoV 2 to invade host cells. Its expression is low in cardiomyocytes and high and specific for pericytes (PER) (Gencer et. al., 2020). These are central nervous system (CNS) cells that make up the blood-brain barrier (BBB) and endothelium of cerebral blood vessels.

Angiotensin II and its type I receptor (AT1) promote vascular wall inflammation, NF kB-mediated adhesion molecule expression, cytokine and chemokine release, and increased oxidative stress. These factors contribute to endothelial dysfunction and the recruitment of arterial leukocytes in the development of atherosclerotic plaques (Gencer et. al., 2020).

Endothelial dysfunction can be promoted by SARS CoV2 by shifting the balance in the Renin Angiotensin Aldosterone System (RAAS) to the angiotensin II/AT1 axis, in such a way as to elevate oxidative stress and inflammation. Endothelial dysfunction is characterized by decreased nitric oxide levels as a consequence of impaired endothelial nitric oxide synthase function. Nitric oxide is a vasodilator and its deficiency leads to hypertension by constricting blood vessels, which can trigger even more thrombosis and vascular inflammation. In addition to RAAS-mediated effects, emerging evidence has revealed that SARS CoV 2 can also directly cause endothelial dysfunction by infecting endothelial cells (Gencer et. al., 2020).

Activation of the inflammatory and thrombotic mechanism by SARS-CoV-2. The infection is related to an increase in inflammatory cytokines and coagulation disorders, with a predisposition to thrombus formation. PAR: protease-activated receptor; TLR4: Toll-like receptor 4; ttp: activated partial thromboplastin time; PT: prothrombin time; IL: interleukin; TNFα; tumor necrosis factor-α (Figure 2).

Figure 2 - Activation of the inflammatory and thrombotic mechanism by SARS-CoV-2.



Source: Pamplona (2022).

Current rates of thromboembolic events demonstrate the importance of post-discharge surveillance and, potentially, extended post-discharge thromboprophylaxis (Giannis et.al., 2020). The incidence of complications is approximately 30% of

arterial and venous thromboembolic events of COVID-19. The hypercoagulability profile is composed of elevated levels of D-dimers and fibrinogen, prolonged prothrombin time (PT) and mild thrombocytopenia (Almyroudi & Dimopoulos, 2020). D-dimer being evidenced in 33.32% of the total articles analyzed.

A simple and inexpensive biomarker to identify a high-risk subpopulation with latent systemic microvascular damage, regardless of respiratory symptoms, is schistocytes. There was 87.5% evidence of myocardial injury in all with schistocytes ≥ 1%. Thus, the in vivo evaluation of diffuse endothelial damage with formation of fibrin thrombi can be performed through the presence of schistocytes (Della Rocca et al., 2021).

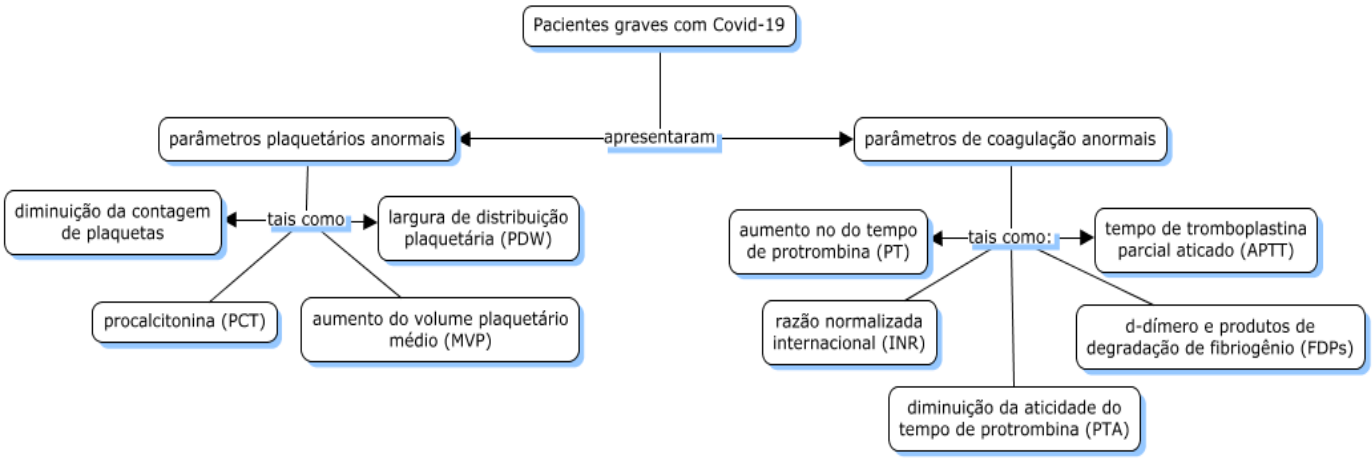
At any stage of disease severity, regardless of pulmonary involvement, one can observe their presence and an increase in high-sensitivity troponin T (7 in 10; 70.0%). Because of this, hypercoagulability may explain the variety of clinical manifestations such as myocardial infarction with normal coronary arteries, neurological manifestations and purpura (Della Rocca et al., 2021).

During inflammation, the Tie2 antagonist angiopoietin-2 (Angpt-2) is released from activated endothelial cells and inhibits Tie2, promoting a prothrombotic phenotypic shift because the endothelial surface is anticoagulant (Schamier et. al., 2021).

SARS-CoV-2 and its Spike protein directly increase platelet activation, through the binding of PAC-1, expressed by CD62P secretes the α granule, causing the release of dense granules to occur and have platelet spread and clot retraction in vitro (Zhang et.al., 2021). Furthermore, increase the plasma concentration of P-selectin that can reduces significantly after the platelets removal (Agrati et. al.,2021).

The release of clotting factors, the secretion of inflammatory factors and the formation of leukocyte-platelet aggregates are facilitated by direct stimulation of SARS-CoV-2 and spike protein on platelets. Serine transmembrane protease 2 (TMPRSS2), proteolytically cleaves and activates the Spike protein to facilitate SARS-CoV-2 virus cell membrane fusions (Zhang et.al., 2021).

Figure 3 - Parameters in critically ill patients with Covid-19.



Source: Pamplona (2022).

TF cells (residual factor) and MVs (precoagulant microvesicles) in patients with COVID-19 were two to four times higher than HS ($p < 0.0001$). As well as P-selectin and PLA. The residual TG correlates with the severity of the disease (Canzano et al., 2020).

For Christopher (Freda et. al., 2021):

The endothelial cell gC1qR, receptor of the globular head of C1q, acts in the regulation of inflammatory and thrombotic responses observed during vascular pathologies, it was decided to investigate how the structural proteins SARS-CoV-2 interact with the endothelial cells gC1qR. In the study, SARS-CoV-2 structural proteins together with endothelial cell culture and gC1qR expression show rapid and significant changes in the expression of molecules that are related to inflammatory and thrombotic progression. Our data also further support the role of the gC1qR, and specifically the C1q binding site on the gC1qR, as a docking receptor for viral proteins.

4. Conclusion

In conclusion, systemic endothelial cell injury driven by SARS CoV 2 increases the threat of multi-organ failure, and patients suffering from impaired endothelial function due to underlying conditions such as CVDs are at a much greater risk of serious complications from COVID 19 (Gencer et. al., 2020). SARS CoV 2 can impair endothelial function by several mechanisms, including endothelitis induced by direct viral infection and endothelial injury, leading to changes in the angiotensin II/AT1 axis and host inflammatory response.

For future work, we recommend further study of vaccines in their study phases, in addition to the pathophysiology and ways of interfering with the cytokine storm and the mechanisms that cause greater comorbidity and mortality from the virus, such as endothelial dysfunction. We also suggest that new drugs be studied to help prevent complications and sequelae of the disease.

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Pamplona M. (2022). Figure 1. PRISMA study selection and inclusion process flowchart.

Pamplona M. (2022). Figure 2. Activation of the inflammatory and thrombotic mechanism by SARS-CoV-2.

Pamplona M. (2022). Figure 3. Parameters in critically ill patients with Covid-19.

Pamplona M. (2022). Table 1: Search Strategy.

Pamplona M. (2022). Table 2: Bibliographic search results table.

Pamplona M. (2022). Table 3. Thrombotic Complications.

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