

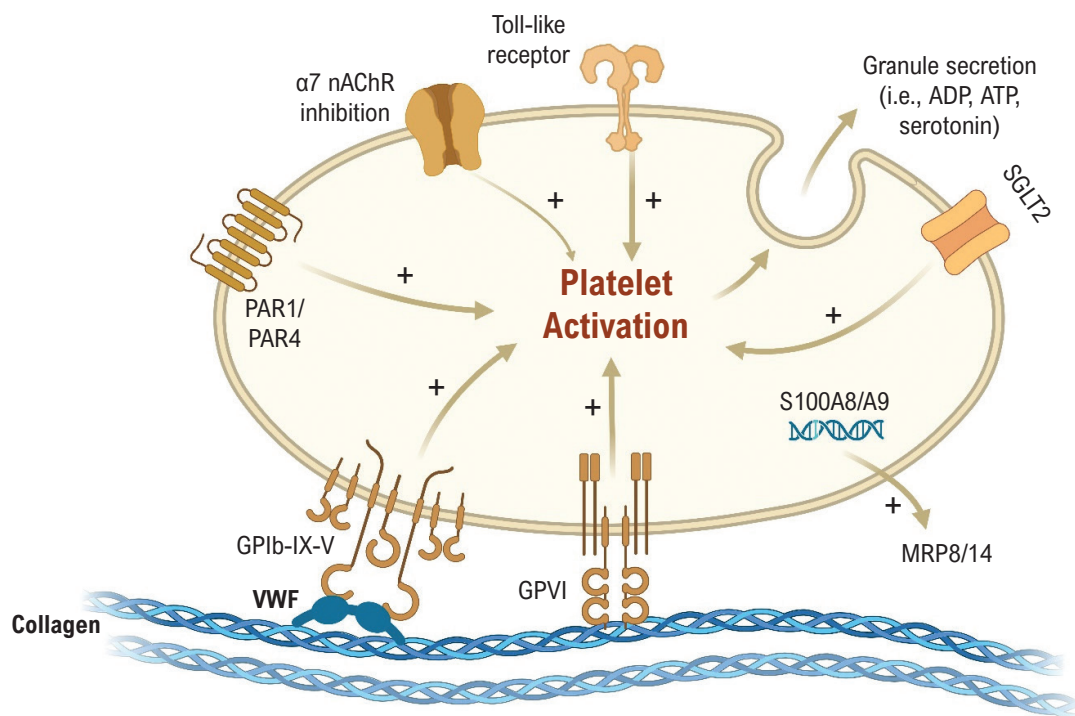
The Role of Platelets in Long COVID Development: A Literature Review

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Central Illustration: The Role of Platelets in Long COVID Development: A Literature Review



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Potential platelet targets in long COVID. ADP: adenosine diphosphate; ATP: adenosine triphosphate; GP: glycoprotein; MRP8/14: myeloid-related protein 8/14 (calprotectin); nAChR: nicotinic acetylcholine receptor; PAR1/PAR4: protease-activated receptor 1/4; SGLT2: sodium-glucose transport protein 2; VWF: von Willebrand factor. Created in BioRender. Lima, G. (2025) <https://BioRender.com/f4t1u82>

Keywords

Blood Platelets; Post-Acute COVID-19 Syndrome; SARS-CoV-2; Thrombosis; Inflammation.

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Abstract

At its peak during the pandemic, coronavirus disease 2019 profoundly impacted global populations and introduced numerous post-infection complications, collectively referred to as long coronavirus disease. The mechanisms underlying the syndrome's chronicity are multifaceted; however, a notable aspect of long coronavirus disease pathophysiology is its intricate association with platelets. The chronic inflammatory response triggered by severe acute respiratory syndrome coronavirus 2 is closely related to platelet activity,

wherein inflammatory molecules bind to specific platelet receptors, inducing the release of platelet granules containing procoagulant and proinflammatory molecules. Consequently, there is a marked elevation in coagulation-related proteins, fostering the development of abnormal microthrombi and a dysfunctional fibrinolytic system. All these changes are indicative of an imbalance in coagulation regulation. Therefore, investigating pharmacological targets linked to this process is crucial for syndrome management, aiming to enhance the quality of life for affected individuals. This review aimed to highlight the importance of platelet function and activity in the pathophysiology of long coronavirus disease, as well as to identify molecular targets directly related to long coronavirus disease or coronavirus disease 2019-related disturbances in platelet homeostasis.

Introduction

In December 2019, a novel variant of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) emerged, causing acute pneumonia among the Chinese population and rapidly gaining global attention.¹ Belonging to the *Sarbecovirus* subgenus within the *Orthocoronavirinae* subfamily, it is a single-stranded RNA pathogen ranging in size from 70 to 170 nm. Its structure features an envelope adorned with glycoprotein spikes derived from the spike protein, giving it a crown-like appearance.^{2,3} This agent is responsible for coronavirus disease 2019 (COVID-19), characterized by its rapid spread via aerosol particles capable of prolonged suspension in the air and on surfaces, thereby explaining the exponential rise in infections.⁴ By January 2020, there were 14,568 confirmed cases and 369 deaths. Given the virus's high transmissibility, the World Health Organization proceeded to declare a pandemic on March 11, 2020. While daily confirmed cases surpassed one million by October 2020,⁵ the global tally continued to climb, reaching over 777 million confirmed cases and more than 7 million deaths by December 8, 2024.⁶

The immune response to SARS-CoV-2 infection occurs in a similar way when compared to other viral infections, and platelets play an essential role in the pathogenesis of COVID-19, given their relationship with the inflammatory process. These cellular fragments maintain vascular function and structure through their interaction with constituent cells of the endothelium and leukocytes.⁷ Within an inflammatory context, these interactions facilitate platelet hyperactivation, exacerbate proinflammatory effects through cytokine release,⁸ activate endothelial cells, and promote the formation of neutrophil extracellular traps.⁹ Furthermore, the formation of microthrombi, although initially harmful to the organism, may serve to contain macrophage-dependent inflammation.^{10,11}

Long coronavirus disease 2019 (long COVID) is a syndrome related to the persistence of symptoms after the acute phase of COVID-19, associated with shortness of breath, joint pain, fatigue, tissue damage, and coagulopathies. Depending on the duration, it can be divided into acute post-COVID (symptoms persist between 3 and 12 weeks) and chronic COVID (symptoms last longer than 12 weeks).⁷ The condition is related to significantly increased concentrations of von Willebrand factor (VWF), platelet factor 4, serum amyloid

A, α -2 antiplasmin (α 2AP), endothelial leukocyte adhesion molecule 1, and platelet endothelial cell adhesion molecule in the soluble part of the blood.¹² It is crucial to emphasize that in long COVID, the virus can be detected within extracellular vesicles (EVs), which underscores its ability to evade the immune system and the potential for renewed infection of multiple tissues and organs, thereby contributing to the symptomatic presentation of the syndrome. These manifestations are attributed to lymphopenia, characterized by a decreased count of T and B lymphocytes stemming from severe acute COVID-19.⁷ Among the manifold physiological alterations associated with long COVID, thrombocytopenia and coagulation abnormalities have been identified as important aspects. This review aimed to compile the main evidence on changes in platelet function in patients with long COVID, as well as identify promising pharmacological targets to counteract platelet hyperactivity in long COVID.

Methods

This article presents a literature review aimed at compiling the main evidence on changes in platelet function in patients with long COVID. The references used were identified by means of a systematic search in the PubMed database using "Platelets" and "Long Covid" as descriptors. To organize and filter the records, an Excel spreadsheet was created, divided by year (2020 to 2024), where publications were categorized by title, abstract, affiliated institution, DOI, and publication date. Article selection for the review was based on this table. In total, 218 records were identified. Of these, 210 articles in English and Portuguese were screened by title and abstract, and 104 were assessed by full text. After full-text evaluation, 90 were included in the review, and 14 were excluded. The inclusion criteria were studies emphasizing platelet and coagulation disorders during both the acute phase of COVID-19 and long COVID. Exclusion criteria consisted of studies unrelated to COVID-19, other aspects of COVID-19 without relevance to platelet dysfunction, or unavailable articles. The search was conducted between October 2023 and December 2024, covering publications released from January 2020 to December 2024. The review flowchart is presented in Figure 1. A table summarizing the potential pharmacological targets in platelets during long COVID, along with the main findings for each molecular target (Supplementary Table 1), was developed. Additionally, a Central Illustration was created to visually highlight these potential targets in platelets.

COVID-19 or SARS-CoV-2 infection

The spike protein is the primary virulence factor of SARS-CoV-2, playing a crucial role in the pathogen's interaction with angiotensin-converting enzyme 2 (ACE-2), a transmembrane protein that converts angiotensin I into angiotensin II, a peptide regulating blood pressure and vasoconstriction.¹³⁻¹⁶ ACE-2 is predominantly expressed in the respiratory tract epithelial cells (alveoli, trachea, bronchi), monocytes, and alveolar macrophages.^{17,18} Additional viral entry mediators include transmembrane serine protease 2, also detected in abundance in cells of the respiratory tract.¹⁹ Like other coronaviruses, SARS-CoV-2 enters target cells via viral envelope cell

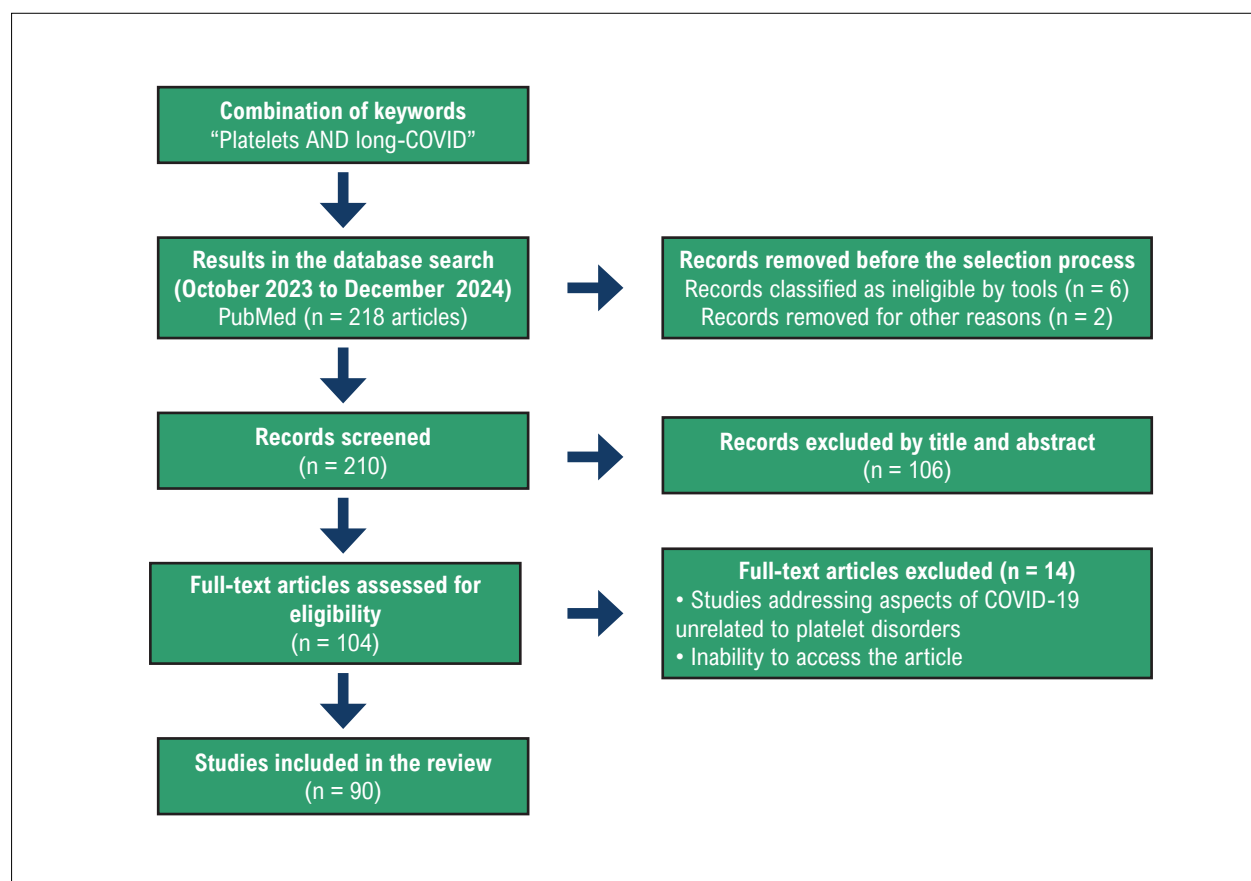


Figure 1 – Flowchart of the selection process for studies included in the review.

membrane fusion and subsequent endocytosis of its genetic material, releasing the nucleocapsid into the cytosol to initiate RNA replication.²⁰

The immune response to SARS-CoV-2 mirrors that of other viral infections. The innate immune response takes place through the action of type 1 interferons (IFN- α and IFN- β), macrophages, neutrophils, and natural killer cells, whereas adaptive immunity relies on CD8⁺ cytotoxic and CD4⁺ helper T cells.²¹ Th1-dominant responses enhance CD8⁺ T cell activation and viral control, whereas Th2-biased responses, which promote B cell activation and antibody production, correlate with severe COVID-19.²²

Systemic viral dissemination occurs through the circulatory system via the release of EVs containing the spike protein by host cells, a condition that permits infection of other cells that express the ACE-2 receptor and transmembrane serine protease 2, including renal, intestinal, and cardiovascular cells, glial cells, and neurons.¹⁹ In this manner, the virus infects multiple organs beyond the respiratory tract, leading to varied clinical manifestations including neurological symptoms, such as headache, confusional states, stroke, and cerebrovascular diseases; respiratory symptoms, such as dyspnea, dry cough, and pneumonia; micro-thrombotic events; anosmia; renal complications, such as kidney injury and nephritis; cardiovascular complications, such as pulmonary embolism,

acute myocardial infarction, deep vein thrombosis, and heart disease; gastrointestinal disorders, such as emesis and diarrhea; and dermatological disorders, such as erythematous and urticarial rashes. In addition to the acute conditions of COVID-19, chronic manifestations such as delirium, persistent cough, dyspnea, chest pain, anosmia, ageusia, diabetes, diarrhea, abdominal pain, dystonia, fatigue, loss of appetite, fever, and thrombotic events have also been observed.²³

Despite the relatively low mortality rate of SARS-CoV-2 infection, attention now turns to survivors experiencing persistent symptoms, known as long COVID.²⁴ These symptoms, although not life-threatening, significantly impact patients' quality of life.²⁵ In this context, long COVID encompasses a broad spectrum of debilitating conditions following documented viral infection, with a global prevalence estimated to affect at least 10% of infected individuals, totaling approximately 76 million cases.^{26,27} These circumstances contribute to the overall impact of the pandemic on both the physical and mental health of society.

Molecular mechanisms of platelet activation in COVID-19 and long COVID: Emerging therapeutic targets

Platelets are cytoplasmic granular fragments essential for maintaining hemostasis, playing a central role in the formation of the primary hemostatic plug following endothelial injury.²⁸

Under conditions of high shear stress, VWF located within the subendothelium and adsorbed onto adhesive proteins of the vascular wall facilitates platelet adhesion through its interaction with the glycoprotein (GP) Ib-IX-V complex. The stability of this adhesion is further reinforced by integrins such as $\alpha 2\beta 1$, $\alpha 5\beta 1$, and $\alpha 6\beta 1$, which interact with extracellular matrix components including collagen, fibronectin, and laminins. Additionally, the $\alpha \text{IIb}\beta 3$ integrin plays a crucial role by mediating stable platelet adhesion through its binding to both VWF and subendothelial fibronectin. Simultaneously, the interaction between collagen and platelet GPVI triggers intracellular signaling pathways that further enhance platelet activation.²⁹

These molecular events culminate in cellular responses essential for consolidating primary hemostasis, including the recruitment of vasoactive molecules, platelet activators, and factors that promote enhanced platelet-endothelium interactions. Negative feedback mechanisms, predominantly mediated by nitric oxide and prostacyclin, serve to limit this activation, preventing the formation of excessive platelet aggregates and reducing the risk of thromboembolic events. However, this finely regulated balance can be significantly disrupted during systemic inflammatory conditions, such as COVID-19 and long COVID, where the coagulation cascade may be aberrantly triggered by elevated levels of proinflammatory cytokines.⁷ Concurrently, fibrinolytic activity is often suppressed due to increased concentrations of plasminogen activator inhibitor type 1.^{30,31} It is also important to highlight that dysregulation of coagulation can perpetuate and amplify the inflammatory response, creating a deleterious feedback loop between coagulation and inflammation.³²

Within this regulatory framework, inflammation and platelet activation become intricately linked. Inflammatory mediators bind to specific platelet receptors, including P-selectin, GPIb, GPVI, GPIIb-IIIa, and CD40L, triggering platelet degranulation and the release of proinflammatory and procoagulant molecules. These receptors also play pivotal roles in leukocyte recruitment and modulation of vascular permeability, further exacerbating the inflammatory milieu.³³ This process is particularly evident in COVID-19, where elevated levels of prothrombotic mediators such as fibrinogen, VWF, and D-dimer are consistently observed, indicating significant involvement of endothelial cells, platelets, and the coagulation system in the development of thromboinflammatory complications.⁹

Studies have demonstrated a hyperactive platelet phenotype in COVID-19, characterized by elevated markers of platelet activation and an inflammatory, prothrombotic transcriptome profile.³⁴⁻³⁹ These hyperreactive platelets release factors that intensify both inflammation and hypercoagulability within the endothelium. Moreover, direct interaction between SARS-CoV-2 and primary megakaryocytes induces the expression of S100A8/A9 (calprotectin), suggesting that the virus may promote inflammatory changes in both megakaryocytes and circulating platelets through direct and indirect mechanisms.⁹

As a result, vascular alterations, disseminated intravascular coagulation, and large-vessel thrombosis emerge as critical determinants of poor prognosis in affected patients.^{40,41} Endothelial dysfunction stands out as a major factor associated with disease severity and mortality,⁴² contributing

to vascular inflammation, coagulopathy, and pulmonary microthrombus formation.^{42,43} Dysregulation of both coagulation and fibrinolysis is evidenced by markedly elevated fibrin degradation products and the persistent presence of plasma protein products during both acute COVID-19 and long COVID phases. Notably, an increase in $\alpha 2\text{AP}$, a key fibrinolysis inhibitor, further exacerbates this imbalance, contributing to fibrinolytic shutdown and enhancing the risk of severe complications, including resistance to plasminogen activator-based therapies and potentially increasing SARS-CoV-2 virulence.⁴⁴

During the acute phase of infection, high levels of inflammatory markers such as interleukin (IL)-6, IL-8, IFN- α , IL-18, IL-1 receptor antagonist, monocyte chemoattractant protein, and macrophage inflammatory protein 1 α are commonly observed, with gradual declines over time. Nonetheless, even recovered patients across all severity categories continue to exhibit elevated levels of growth factors, such as platelet-derived growth factor-BB (PDGF-BB), brain-derived neurotrophic factor, vascular endothelial growth factor (VEGF)-A, and VEGF-D, compared to healthy individuals. These persistent immunological alterations suggest ongoing chronic inflammation and endothelial repair. Furthermore, prolonged symptoms in post-COVID-19 patients have been correlated with elevated monocyte chemoattractant protein levels during early convalescence and increased PDGF-BB concentrations at later stages (≥ 30 days post-infection).⁴⁵

EVs have also emerged as important mediators in the interplay between inflammation, coagulation, and immune regulation, contributing to complications such as thrombosis.⁴⁶ EVs are capable of carrying viral RNA, which may remain detectable in the nasopharynx even after hospital discharge. This RNA can potentially be redistributed to various tissues and organs via the circulatory system.⁴⁷⁻⁴⁹ Furthermore, the externalization of phosphatidylserine on EV surfaces can initiate inflammatory responses, promote coagulation, and worsen conditions such as hypoxia and endothelial dysfunction,⁵⁰ offering potential mechanistic insights into long COVID pathogenesis.

Complement system dysregulation has been consistently reported in individuals with long COVID. Patients exhibit an imbalance in terminal complement complex (TCC) formation, characterized by increased soluble C5bC6 complexes and reduced generation of C7-containing TCCs capable of integrating into cell membranes. This imbalance suggests heightened complement activity, with preferential TCC deposition on cellular membranes during active long COVID. Such pathological complement activation may underlie typical thromboinflammatory and microangiopathic features, with downstream effects including hemolysis, platelet and endothelial activation, and alterations in innate immune cells, particularly neutrophils.⁵¹⁻⁵³

Conversely, a cross-sectional cohort study conducted in Ohio indicated that complement system activation might not be the primary driver of platelet hyperreactivity observed in post-acute sequelae of SARS-CoV-2 infection (PASC). In this study, platelet-depleted plasma from patients with PASC induced greater platelet activation compared to plasma from healthy controls, even after heat inactivation, suggesting

complement-independent mechanisms.⁵⁴ The study also identified reduced factor Xa levels in platelet-poor plasma from patients with PASC, implying a functional defect in the coagulation cascade within this population.⁵⁴

Persistent endotheliopathy in convalescent COVID-19 patients appears to occur independently of acute phase responses or neutrophil extracellular trap activity and may contribute to long COVID pathogenesis.⁵⁵ Elevated plasma levels of factor VIII activity, VWF antigen, and VWF propeptide have been reported up to two months post-infection, correlating with increased thrombin generation.⁵⁵ Additionally, decreased levels of the VWF-cleaving protease ADAMTS-13 have been observed during convalescence, resulting in an imbalanced VWF/ADAMTS-13 ratio.⁵⁶ This dysregulation is associated with both severe COVID-19 and post-acute sequelae, suggesting a sustained hypercoagulable state.⁵⁷⁻⁶⁰

The $\alpha 7$ nicotinic acetylcholine receptor (nAChR) has emerged as a promising therapeutic target for mitigating hyperinflammatory and thrombotic processes associated with COVID-19. Enhanced vagal stimulation via $\alpha 7$ nAChR improves pulmonary and systemic inflammation, with low $\alpha 7$ nAChR expression correlating with higher C-reactive protein levels and more severe inflammation. Activation of this receptor reduces systemic hyperinflammation, inhibits platelet activation, and attenuates thrombotic pathways, highlighting its therapeutic potential in COVID-19 management. Furthermore, downregulation of choline and its derivatives in COVID-19 patients, especially in severe cases, reinforces the relevance of the $\alpha 7$ nAChR pathway in vascular homeostasis. Cholinergic agonists that stimulate $\alpha 7$ nAChR demonstrate both anti-inflammatory and antithrombotic effects, making them attractive candidates for treating both acute and post-acute COVID-19 syndromes.⁶¹⁻⁶⁵

The C-type lectin-like receptor 2 (CLEC-2) also plays a critical role in platelet aggregation and stable thrombus formation, although it is not required for initial collagen adhesion.⁶⁶ The CLEC2.Fc fusion protein, which combines the extracellular domain of CLEC-2 with the Fc portion of human IgG1, has shown efficacy in inhibiting SARS-CoV-2-induced immunothrombosis *in vivo*, suggesting that targeting CLEC-2 signaling may offer therapeutic benefits for SARS-CoV-2-associated immunothrombosis.⁶⁷ Additionally, CLEC2.Fc has been shown to reduce tumor necrosis factor production and macrophage infiltration in lipopolysaccharide-induced peritonitis models, indicating broader anti-inflammatory effects through the inhibition of CLEC-2 and its ligand, podoplanin.⁶⁸

Another relevant factor in the context of COVID-19-associated vascular dysfunction is the sodium-glucose cotransporter-2 (SGLT2), whose expression is elevated during infection, contributing to cardiovascular injury and amplifying the proinflammatory and prothrombotic state.^{69,70} Evidence suggests that SGLT2 inhibitors, such as empagliflozin, offer endothelial protection by reducing inflammation and oxidative stress and by enhancing vascular regenerative capacity.⁶⁹⁻⁷¹ Consequently, SGLT2 inhibitors are emerging as potential therapeutic strategies for mitigating the vascular complications observed in both acute COVID-19 and long COVID.⁷²⁻⁸⁹

Conclusion

A significant population of SARS-CoV-2 infection survivors continues to experience persistent symptoms into the post-acute phase, known as long COVID. The virus's significant impact on inflammatory modulation and platelet function markedly impairs the health and quality of life of individuals in the aftermath of the pandemic. Among the primary challenges faced by these patients, thrombotic and inflammatory processes have remained prominent concerns. Therefore, this comprehensive literature review aimed to identify and summarize the main molecular targets that may be involved in platelet disorders found in post-COVID syndrome, identifying 10 potential pharmacological targets implicated in the platelet pathophysiology of long COVID. Further studies are warranted to better understand these mechanisms.

Limitations

This study has some inherent limitations due to its design. As a narrative review, it was not possible to conduct an aggregated statistical analysis (meta-analysis), which limits the quantitative precision of the conclusions and reduces the study's statistical power. The review was restricted to specific databases and literature available in certain languages, which may have resulted in the exclusion of relevant publications. It is important to mention that the study only included references from January 2020 to December 2024.

Author Contributions

Conception and design of the research and critical revision of the manuscript for intellectual content: Lima GF, Brito FC; acquisition of data, analysis and interpretation of the data and writing of the manuscript: Lima GF, Miossi L, Silva AGJ, Novais OBP, Brito FC; obtaining financing: Brito FC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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*Supplemental Materials

For Supplementary Table(s), please click here.



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