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Alterations of platelet count, structure, and funtion in COVID-19 and post-COVID-19 vaccination

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ABSTRACT

Background. Platelets play a crucial role in the blood clotting mechanism and changes in platelet count, structure, and function contribute to several thrombotic and hemorrhagic manifestations. This review provides an in-depth analysis of the complex effects of COVID-19 and its vaccines on platelets.

Material and method. We carried out an extensive review of the literature in PubMed and PubMed Central covering various types of research, including original articles, systemic reviews, meta-analyses, and case reports.

Results. Thrombocytopenia attributed to multifactorial mechanisms has been identified in patients with COVID-19 and is associated with an elevated risk of in-hospital mortality. Furthermore, immune thrombocytopenic purpura may manifest in association with COVID-19 infection; potential underlying factors contributing to the etiology of immune thrombocytopenic purpura in COVID-19 include immune dysregulation, molecular mimicry, and cryptic antigen expression. Alterations in the platelet transcriptome that contribute to thrombotic features in COVID-19 patients have also been observed.

Although various platelet abnormalities have also been observed following COVID-19 vaccination, the precise mechanisms remain to be fully elucidated. In addition to immune thrombocytopenic purpura, a specific type of thrombocytopenia termed "vaccine-induced thrombotic thrombocytopenia" has been identified, characterized by the formation of blood clots and a reduced platelet count with the presence of anti-platelet factor 4 antibodies. Rare cases of thrombotic thrombocytopenic purpura have also been described after COVID-19 vaccination, but the exact mechanism remains unclear.

Conclusion. Platelet alterations can be related to both COVID-19 and COVID-19 vaccination. However, post-COVID-19 vaccination alterations are rare and the substantial benefits of vaccination far outweigh these complications.

Keywords: COVID-19, COVID-19 vaccination, platelets, immune thrombocytopenic purpura, vaccine-induced thrombotic thrombocytopenia, thrombotic thrombocytopenic purpura

Introduction

Coronavirus Disease 2019 (COVID-19) is a viral respiratory illness resulting from infection with SARS-CoV-2, and it has had a significant impact on global health, leading to millions of cases and deaths worldwide. COVID-19 can manifest with a range of clinical presentations, from mild respiratory symptoms to severe complications such as acute respiratory distress syndrome (ARDS) and thrombotic events [1]. Thrombotic complications are common in COVID-19 patients and are associated with elevated morbidity and mortality rates. Endothelium damage, antiphospholipid antibodies, inflammation, increased blood viscosity, and genetic thrombophilia mutations are the principal factors believed to increase the risk of thrombosis in patients with COVID-19 [2].

Platelet activation is a key contributor to inflammation and thrombogenesis. Although platelet count is often normal at the initial diagnosis of COVID-19, certain sensitive biomarkers, such as von Willebrand factor activity, soluble P-selectin, and soluble C-type lectin-like receptor-2 are elevated [3].

COVID-19 vaccination has been implemented globally as a key strategy to fight the COVID-19 outbreak and mitigate the impact of the COVID-19 pandemic. Vaccines have been developed utilizing diverse technologies, such as viral vectors and mRNA. These vaccines elicit an immune response and generate neutralizing antibodies against the spike protein of SARS-CoV-2. This protein is expressed on the surface of the virus, allowing it to attach to human target cells and replicate after entry [4,5].

Although COVID-19 vaccination is significantly preventing and reducing the severity of the disease, some cerebrovascular, cardiac, and hemostatic consequences have been reported to occur after COVID-19 vaccination [6-8].

This review aims to present a comprehensive analysis of the impact of COVID-19 and COVID-19 vaccination on platelet count, structure, and function to help elucidate the mechanism of hemostatic complications observed in these conditions. To achieve this, we thoroughly reviewed and summarized the published data concerning these situations in the PubMed and Google Scholar databases.

Platelet alterations in patients with COVID-19

Thrombocytopenia

Thrombocytopenia is a condition characterized by a reduced number of circulating platelets. It has been reported in individuals hospitalized with COVID-19 and found to be closely related to an increased risk of mortality during the hospitalization period. Furthermore, it has been observed that thrombocytopenia was more prevalent among non-survivors as compared to survivors [9-11]. Three mechanisms have been proposed as possible causative factors for thrombocytopenia in COVID-19 patients: decreased platelet production due to direct bone marrow infection, increased platelet destruction by the immune system as a result of the formation of autoantibodies and immune complexes, and increased platelet consumption because of platelet aggregation and formation of microthrombi in the lungs [12]. However, these mechanisms have been proposed based on comparisons with similar viral infections, and they have not yet been clarified.

Immune thrombocytopenic purpura (ITP)

Many cases of ITP have also been observed in symptomatic COVID-19 patients. It typically manifests three weeks after the onset of COVID-19 symptoms in approximately one-fifth of the patients, with numerous cases occurring even after clinical recovery. The development of COVID-19-related ITP is thought to be associated with several factors, including underlying immune dysregulation, susceptibility mutations in the suppressor of cytokine signaling 1 (SOCS1) gene, molecular mimicry, cryptic antigen expression, and epitope spreading. Fortunately, in approximately one-third of the cases, no bleeding signs were observed at diagnosis, and cases of severe life-threatening bleeding were rare [9,13].

Alterations in platelet structure and function

Several recent studies have investigated the influence of COVID-19 on platelets, exploring changes in platelet gene expression, function, and behavior in infected patients. These investigations have revealed alterations in the platelet transcriptome induced by COVID-19, leading to modifications in platelet function that align with the thrombotic characteristics shown in COVID-19 patients [1,14,15]. The circulating

environment in COVID-19 exerts a more profound functional influence on platelets compared to other diseases, potentially impairing their aggregation [14]. Concurrently, COVID-19 patients exhibit elevated platelet activation, as indicated by increased platelet-leukocyte aggregates and elevated P-selectin expression [15]. Furthermore, patients with COVID-19 have displayed changes in their platelet proteome signature and impaired platelet integrin αIIbβ3 activation, suggesting the presence of two distinct platelet populations, one with a modified proteome and diminished functional responses and another featuring P-selectin-expressing neutrophil-associated platelets [16].

Table 1. Platelet Alterations in Patients with COVID-19

Alteration	Description	Proposed mechanism
Thrombocytopenia	Low platelet counts associated with an increased risk of in-hospital mortality; more likely in non-survivors.	Decreased platelet production due to bone marrow infection increased platelet destruction by immune system increased platelet consumption due to platelet aggregation and microthrombi formation
Immune thrombocytopenic purpura (ITP)	Manifests three weeks post-COVID-19 symptoms onset; life-threatening bleeding is infrequent.	Underlying immune dysregulation Susceptibility mutations in SOCS1 gene Molecular mimicry Cryptic antigen expression Epitope spreading
Alterations in platelet structure and function	Changes in platelet gene expression, function, and behavior	Modifications in platelet transcriptome Functional influence of circulating environment Altered platelet proteome signature Impaired platelet integrin αIIbβ3 activation

Platelet alterations associated with COVID-19 vaccination

Vaccine-induced immune thrombotic thrombocytopenia (VITT)

VITT is a rare condition characterized by the simultaneous occurrence of blood clot formation and a decrease in platelet count, with compelling evidence suggesting that VITT represents a vaccine-related variant distinct from spontaneous heparin-induced thrombocytopenia. Many case reports and studies have illuminated the emergence of VITT following COVID-19 vaccination [17-20]. The underlying mechanisms driving the development of VITT remain incompletely understood, but substantial evidence points to platelet consumption and the gradual promotion of clot formation triggered by the generation of antibodies against the protein platelet factor 4 (PF4) [17,21-25]. PF4 is a chemokine primarily found in megakaryocytes and within the α-granules of platelets, and it is released upon platelet activation [26]. In VITT, patients generate IgG antibodies that target the PF4-polyanion complexes, subsequently activating platelets through the Fcγ receptor on their surface. This platelet activation leads to elevated PF4 release, further facilitating the formation of complexes with anti-PF4 antibodies. This sequence of events results in increased platelet aggregation, clot formation, and thrombocytopenia. Nonetheless, the specific triggers for the robust autoimmune response in VITT and the components of vaccines responsible for inducing antibody formation against PF4 remain unknown [27].

Immune thrombocytopenic purpura (ITP)

Some researchers have reported the incidence of ITP following COVID-19 vaccination [19,28]. However, it is uncommon, and the frequency pattern may be associated with the administration scale of individual vaccines and their potency in inducing autoimmunity. In other words, the more potent the COVID-19 vaccine is in provoking an antigenic challenge, the shorter the lag time will likely be. The majority of patients experienced a benign course and exhibited positive responses to standard treatments of primary ITP [29].

Thrombotic thrombocytopenic purpura (TTP)

The classic TTP is a rare, life-threatening condition associated with consumptive thrombocytopenia, microangiopathic hemolytic anemia, and potential damage to

multiple organs. The mechanism of classic TTP involves a severe deficiency of the enzyme ADAMTS13 (a disintegrin and metalloproteinase), which is necessary for cleaving von Willebrand factor, and when unregulated, leads to the formation of abnormal platelet microthrombi [30]. The most common cause of ADAMTS13 deficiency is the development of autoantibodies against ADAMTS13. However, in rare cases, it can be hereditary due to mutations in the ADAMTS13 gene [31]. TTP has also been reported in rare cases following COVID-19 vaccination [32-37]. These studies and case reports provide evidence of a potential association between COVID-19 vaccination and the development or relapse of TTP. The exact mechanisms underlying the development of TTP following vaccination are not fully understood, and further research is recommended to determine epitope similarities, if any, between ADAMTS-13 and SARS-CoV-2 vaccine antigens [38].

Table 2. Platelet alterations associated with COVID-19 vaccination

Alteration	Description	Mechanism
Vaccine-induced immune thrombotic thrombocytopenia (VITT)	A rare condition associated with decreased platelet count and clot formation following COVID-19 vaccination	Triggered by antibodies against PF4, leading to platelet activation and aggregation.
Immune thrombocytopenic purpura (ITP)	A rare condition, mostly benign and responsive to typical ITP treatments.	Autoimmunity triggered by the vaccine's antigenic challenge and varying with vaccine potency
Thrombotic thrombocytopenic purpura (TTP)	A rare condition associated with spontaneous formation of platelet microthrombi, consumptive thrombocytopenia, and organ damage	Not fully understood

Conclusion

Platelet alterations can be a consequence of both COVID-19 and COVID-19 vaccination. However, post-COVID-19 vaccination alterations are uncommon and the substantial benefits of vaccination including disease prevention, reduced transmission, economic recovery, and the lifting of restrictions, far outweigh these complications.

Conflicts of interest: The authors declare that there are no conflicts of interest

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