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SYSTEMATIC REVIEW ON PLATELET AND SARS Cov2 INFECTION

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ABSTRACT

Viral infections are associated with thrombocytopenia due to variety of causes. It is usually caused by enhanced platelet clearance destruction, while in the later parts of SARS-Cov2, hypo-proliferates thrombocytopenia is observed. Platelets can be activated by viral antigen-antibody complexes. In 2019 and 2021 the severe acute respiratory syndrome coronovirus2 (SARS-Cov-2) has swept all-over the world. Eighty per cent of the patients infected by SARS-Cov-2 may be a symptomatic direct viral-platelet interaction and activation; formation of platelet to leukocyte aggregates; FcR- Mediated infraction with immune complexes. Platelets are important in maintaining vascular homeostasis and endothelial integrity in end organs. During Covid-19 infection, platelets are stimulated activated and recreated at the site of infection. They activate inflammatory process and are responsible complications of coagulopathy. The aim of this review is to present the platelets fraction contribution in clinical practice. Here we will provide a comprehensive review of the history and the current state of the artificial platelet approaches along with discussing the translational challenges and opportunities

INTRODUCTION

Platelets were discovered by G.Bizzogero in 1882 and rediscovered in 1960s after many decades of oblivion. Platelets express a number of iron channel subtypes that are known to be essential for the core activities of excitable cells but which have less well established function in blood cells. Platelets are to contribute a number of processes beyond homeostasis in physiologically such as immunity and angiogenesis. Most of the reviews are considering the ultimate possibility that iron homeostasis represent targets for disease treatment. The platelets exert their influence in variety of ways which are discussed extensively in these reviews.

METHODS

Past published literatures have been reviewed using Googly scholar and PubMed, focusing on the diagnosis of platelets and SARS Cov2 infection. This search includes trials; meta-analysis reviews government publications guidelines and journal articles published with the keywords “Platelets and SARC Cov2 infections” in the title and screening in the title or abstract. Also we reviewed studies pertaining to epidemiology, ant pathogenesis, and consumptive coagulopathy and pro-inflammatory molecules and hyper activated in Covid-19.

DISSCUSSION

Platelets being numerous in comparison to other components may be first to internalize virus and show a response, similar to influenza, another similar single-stranded viral RNA virus. They secrete many inflammatory mediators and may be

prone to release certain inflammatory molecules, chief of which are IL-1β, IL-18, CD40L, and thromboxane A2 and B_2, IFN α and γ. Experiments to evaluate the levels of these elaborated cytokines termed a cytokine storm showed reduced levels for some in non-severe disease like G-CSF, IL-1α, 2, 4, 5, 6, 10, 22, TGF-α, and VEGF and increased in some in severe disease like those mentioned above. [1]

Viral infections are associated with thrombocytopenia due to a variety of causes. It is usually caused by enhanced platelet clearance/destruction, while in the later parts of SARS-Cov2, hypo proliferative thrombocytopenia is observed. Platelets can be activated by viral antigen-antibody complexes, host inflammatory responses, reduce platelet synthesis by acting on megakaryocytes. [5] Thrombocytopenia is observed as a deregulated host response in sepsis usually seen after viral infection. [3]

Many mechanisms are responsible for the thrombocytopenia observed, which include clearance by reticular endothelial system; activation by increased thrombin generation and consumptive coagulopathy; Direct viral-platelet interaction and activation; formation of platelet-leukocyte aggregates; FcR-mediated interaction with immune complexes; Platelet clearance due to increased endothelial damage; Platelet autoantibody formation, with subsequent platelet clearance; Splenic/hepatic sequestration; Marrow/megakaryocyte suppression - due to inflammatory response, direct viral infection and reduced thrombopoietin. Complex mechanisms underlay thrombocytopenia maybe due to inflammation, reperfusion injury triggered by the infection. [5]

Platelet vesicles and granules (alpha- and dense-granule) are measured by values of PF4 and serotonin respectively. A study revealed reduced levels of both PF4 and serotonin in platelets from non-severe and severe cases of COVID-19. Consequently, these parameters were increased in plasma. [1]

Platelet activation is dependent on stimulatory and inhibitory PKC signalling pathways. Of these, PKCδ is a key regulator of platelet granule secretion, activation, and aggregation activity. [1] PKCδ phosphorylation was measured in response to thrombin in patients with severe and non-severe COVID-19, in which they were increased. It was undetectable in non-infected cases. [1] Number of adherent platelets was increased in severe patients compared with non-severe patients and controls, indicative that platelets are hyperactive, express pro inflammatory molecules and hyper activated in COVID-19. [1]

Surface receptor on platelet for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), and viral internalization is by receptor-mediated endocytosis, micro pinocytosis, and phagocytosis of fragments from apoptotic cells. [2] Viral RNA may activate platelet TLR-7. This leads to AKT- and p38-dependent α-granule content release. Consequently, this leads to interaction of platelets with neutrophils via P-selectin and CD40L. This leads to release of C3 and GM-CSF, which leads to NETosis. [7] Neutrophil extracellular traps (NETs) protect from viral infection but are also highly prothrombotic and, if this C3–NET–GM-CSF response is deregulated, induce intravascular coagulation. Uncontrolled NETosis can cause severe cell and organ damage. Thrombin thus activated releases C3 and the cycle of complement cascade. Patients with COVID-19 also show markers for NETosis. This process mostly occurs at start of infection. Increased C3 and GM-CSF were reported in patients with COVID-19.

Platelets are important in maintaining vascular homeostasis and endothelial integrity in end organs. Infected endothelium in small vessels with slower blood flow can develop thrombosis, both venous (venous sinus thrombosis and deep vein thrombosis) and arterial (myocardial infarction and stroke). [3] Cytokines can directly affect platelets and contribute to thrombotic activity. Exposure of whole blood to IL-6 and IL-1b, IFN, TGF may lead to increased hypercoagulability and other changes that also affect other blood components in addition to platelets.

Majority of severe cases of COVID-19 show thrombocytopenia. Platelet count has been found to be much lower in severe cases than in non-severe cases. [2] During COVID-19 infection, platelets are stimulated, activated and recruited at the site of infection. They activate inflammatory process, and are responsible for complications of coagulopathy. Larger platelets contain higher numbers of dense granules and vesicles, and therefore are believed to be more reactive than smaller platelets. [2] There is also increased mitogen-activated protein kinase (MAPK) pathway activation.

Deregulation of blood platelet activation occurs via alterations in the function of angiotensin converting enzyme (ACE), the angiotensin II/angiotensin type 1 receptor: a G-protein coupled receptor and proteinase-activated receptor 1 (PAR1). [2]

Other parameters like D-dimer, fibrinogen, PT and PTT also show changes. Lower platelet, higher d-dimer and fibrinogen have been found to be risk factors for assessing severity of COVID-19. Thrombocytopenia is detected in many COVID-19 patients (the incidence varying dependent on severity) and it is usually mild (100–150 ×109 /L). Mild thrombocytopenia has been

detected in 60–95% of severe cases of COVID-19. Thrombocytopenia was more likely to occur in severe cases than in survivors. [4] Severe thrombocytopenia is rarely reported in COVID-19 patients, for example with an ITP-like state. Patients with thrombocytopenia also were found to be more likely to be elder, male more than female, lower absolute neutrophil and lymphocyte counts, higher C-reactive protein (CRP) than those without thrombocytopenia. A temporal trend of dropping platelet counts in patients with COVID-19 could suggest a worsening thrombotic state. [5]

COVID-19 patients with thrombocytopenia had larger mean platelet volume than those with normal platelet counts. There is increased production of large immature platelets and circulating activated platelets. Platelets thus contribute to thrombi-inflammation, and the inhibition of pathways related to platelet activation may be effective therapeutic targets in treatment of COVID-19. [1]

RNA sequence analysis indicates that human platelet transcriptome is altered during SARS-CoV-2 infection. Plasma thrombopoietin (TPO) levels have been found to be increased in all COVID-19 cases. Platelet morphology and ultrastructure from both non-infected cases and COVID-19 patients have been found to have similar appearances (open canicular system, alpha and dense granules, mitochondria, and microtubule system). Basal P-selection surface expressions on neutrophils were increased in all COVID-19 patients independent of severity. Platelet aggregation has also been found to be increased in COVID-19 patients. [7]

CONCLUSION:

Known facts indicate that inflammation, hyper coagulation, and thrombosis are hallmarks of severe coronavirus disease 2019 (COVID-19). Platelets are a great source of inflammatory mediators. From the systematic review, it can be concluded that SARS-CoV-2 RNA molecules are associated with human platelets. Platelets are hyper activated in COVID-19, both in non-severe and severe forms of the disease. Platelets have enhanced adhesion molecules, alpha and dense granule contents are elevated in blood, and they cause cytokine storm.

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