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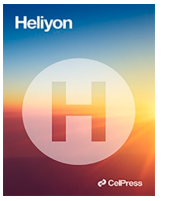

Review article

Viruses and thrombocytopenia

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ABSTRACT

Thrombocytopenia, characterized by a decrease in platelet count, is a multifaceted clinical manifestation that can arise from various underlying causes. This review delves into the intriguing nexus between viruses and thrombocytopenia, shedding light on intricate pathophysiological mechanisms and highlighting the pivotal role of platelets in viral infections. The review further navigates the landscape of thrombocytopenia in relation to specific viruses, and sheds light on the diverse mechanisms through which hepatitis C virus (HCV), measles virus, parvovirus B19, and other viral agents contribute to platelet depletion. As we gain deeper insights into these interactions, we move closer to elucidating potential therapeutic avenues and preventive strategies for managing thrombocytopenia in the context of viral infections.

1. Introduction

Platelets, characterized by their lack of a nucleus and small size, exhibit a multitude of functions while having a limited lifespan [1]. The process of producing platelets, known as thrombopoiesis, predominantly occurs in the bone marrow. Hematopoietic stem cells are differentiated into polyploid megakaryocytes, which are big cells with a diameter of 50–100 μm. Proplatelets, which are lengthy, branching cytoplasmic protrusions, are released by these megakaryocytes [2]. A complicated mechanism is involved in the change from megakaryocytes to platelets. Despite extensive research on the basic mechanics of platelet synthesis, ongoing studies aim to identify the precise molecular regulators and cellular processes involved in platelet generation and release [3].

In the human circulatory system, platelets persist for approximately 7–10 days, and subsequently, platelet clearance predominantly occurs within the spleen and liver [1]. The liver produces thrombopoietin, which regulates the production and maturation of megakaryocytes in the bone marrow by stimulating the megakaryocytes' thrombopoietin receptor. Proplatelet production is sparked by this activation, especially when the bloodstream's platelet count is low [4]. The daily production and elimination of 10^{11} platelets by the human body maintains a normal steady-state platelet count. The generation of platelets needs to be tightly controlled to prevent

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spontaneous bleeding, artery blockage, and organ damage. Numerous complex systems regulate the elimination and formation of platelets in both normal and pathological circumstances [5].

Several approaches are used to mediate platelet clearance. One such approach works by using the aging (senescence) signals brought on by glycan degradation and apoptotic events. Additionally, immunological responses, more notably antibody reactions, can destroy platelets [5]. Platelet clearance is mediated by the presence of glycans on the surface of platelets [6,7]. In recent studies, the absence of sialic acid on the surface of platelets appears to contribute significantly to the recognition and elimination of senescent platelets from circulation [8]. The hepatic Ashwell-Morrell receptor (AMR) aids in the clearance of sialic acid that is lost from platelets during circulation. The transmembrane heteroligomeric glycoprotein complex, also known as the AMR, is in charge of identifying and seizing platelets for expulsion [9]. Moreover, antibodies can induce platelet desialylation, which leads to the convergence of signals for platelet removal, combining immune-mediated platelet elimination [5]. Furthermore, in both clinical and experimental viral infections, activated platelets and heightened platelet-leukocyte aggregates are detected. The dynamics and consequences of platelet–leukocyte interactions hinge on the specific leukocyte involved, as well as the nature of the pathogen and the prevailing pathological conditions [10]. Moreover, platelets are capable of interacting with bacterial LPS and subsequently forming platelet leukocyte aggregates (PLAs). Increased PLAs are pivotal in the development of thrombotic conditions. Nonetheless, platelet-monocyte aggregates (PMAs) have been identified as a more responsive indicator of platelet activation compared to platelet-neutrophil aggregates (PNAs) and the expression of platelet surface P-selectin (CD62P) [11,12]. The functional role of E-cadherin expression in platelets is probably associated with its capacity to facilitate interactions between platelets and extracellular factors. These factors, such as fibrinogen, play a role in influencing the formation and stabilization of platelet clots [13]. Moreover, while circulating in a quiescent state, platelets express various receptors, including glycoprotein (GP) Ib-IX-V, GPVI, and α2β1. These receptors have the capability to bind to collagen and von Willebrand factor (VWF) present on damaged endothelial surfaces, facilitating platelet adhesion and activation at injury sites. The formation of a stable clot is contingent upon thrombin generation and platelet-secreted factors like adenosine diphosphate (ADP) and thromboxane A2 (TxA2). These factors play crucial roles in promoting platelet spreading, aggregation, plug formation, and clot retraction [13]. Despite this knowledge, numerous questions remain regarding the precise mechanisms that govern platelet numbers [5].

Platelets play a crucial role in the regulation of bleeding (hemostasis) when a blood vessel wall sustains an injury, leading to the disruption of the endothelial cell layer and exposing the underlying extracellular matrix [14]. In their resting state, circulating platelets exhibit a discoid shape and remain uninvolved in any interactions with the intact vessel wall [15]. Furthermore, they serve vital functions beyond thrombosis and wound healing, as they actively participate in inflammation, immunity, and cancer biology [16]. While platelets are mainly understood to be important participants in thrombosis, growing evidence suggests that they also play a substantial role in immunological responses and inflammatory processes in both healthy and pathological states. The importance of platelets' immunological and inflammatory capabilities, which go beyond their conventional involvement in clot formation, is now well understood [17]. Risk of bleeding is increased after platelet numbers drop below 50, or mostly below 20. It is remarkable to normal platelet numbers are much high, indicating that much more platelets circulate than is needed for hemostasis.

Moreover, the interaction between platelets and endothelial cells has been the subject of substantial investigation due to the serious health effects associated with atherosclerosis [18]. In a state of homeostasis, the endothelium plays an active role in preventing coagulation [19]. This is particularly noteworthy, as microvascular thrombosis is a clinical characteristic observed in numerous viral infections [20]. Endothelial cells synthesize and present heparan sulfate proteoglycans in the glycocalyx. These proteoglycans have the capability to bind to anti-thrombin III, facilitating the inhibition of thrombin molecules produced during the coagulation cascade [19]. Furthermore, endothelial cells play a crucial role in preserving blood fluidity by deactivating thrombin, which, in turn, prevents platelet activation. Additionally, these cells generate and store von VWF in Weibel–Palade bodies. VWF, a sizable multimeric glycoprotein, is instrumental in various coagulation processes, including enhancing the interaction between platelets and collagen within the basement membrane [19].

2. Pathophysiology of thrombocytopenia

According to the standard definition, thrombocytopenia is characterized by a platelet count below $<150{,}000/mm^3$, with severe thrombocytopenia classified as a platelet count below $<50{,}000/mm^3$ [21]. Thrombocytopenia is a prevalent issue that impacts a significant portion of patients in both medical and surgical intensive care units, affecting approximately 40%–50% of individuals [22]. The most frequently observed coagulation disorders in intensive care unit (ICU) patients involve abnormalities in both platelet number and function. Moreover, thrombocytopenia is the prevailing coagulation issue encountered in ICU [21].

Platelets play a crucial role as the initial defense when the endothelial surfaces of blood vessels are damaged. This damage exposes various components like tissue factor, collagen, and von Willebrand factor (vWF) in the subendothelial layer, which initiate platelet aggregation mediated by fibrinogen and vWF. In a rapid sequence, platelets undergo shape change, degranulation, and surface phospholipid exposure, leading to the generation of small amounts of thrombin. This, in turn, triggers the amplification of the clotting process [21]. Activated endothelial release VWF from Weibel Palade bodies into circulation and platelets can adhere to activated VWF.

The primary factors leading to a reduced platelet count involve two major mechanisms: decreased production and increased destruction of platelets. Examples of decreased production include bone marrow failure syndromes, while increased destruction can occur in conditions like disseminated intravascular coagulation (DIC),thrombotic microangiopathies, and increased antibody mediated platelet clearance. Thrombocytopenia, the condition characterized by low platelet count, encompasses a range of underlying mechanisms. Although less common, platelet sequestration and hemodilution also contribute to thrombocytopenia. Furthermore, increased destruction is observed in conditions such as thrombotic microangiopathies and immune thrombocytopenia (ITP) [5,23].

Table 1
Different viruses and their mechanisms of causing thrombocytopenia.

Virus	Mechanism	Reference
SIV	Increase in tumor growth factor (TGF) β	[29]
	Altered thrombopoietin (TPO) production in the liver (TPO production)	
HCV	Directly prevent the generation of TPO by destroying liver tissue	[36]
	Megakaryocyte formation is slowed by decreased TPO production	
	Autoantibodies	
	Hypersplenism	
	Virus-induced bone marrow suppression, and reduced thrombopoietin production	
HHV7	Affecting the megakaryocytes' capacity to survive and differentiate	[29]
HHV6	Hindering the development of TPO-inducible megakaryocytic colonies	[29]
DHF	The interaction of the DENV NS1 protein with platelet-expressed TLRs 4 and 2 initiates platelet activation, leading to aggregation, adhesion to endothelial cells, and the induction of macrophage phagocytosis	[53]
	Antibody binding to DENV activates platelets in a way that is FcgRIIa-dependent, resulting in increased endothelial permeability	[33,51, 52]
	Potentially causing thrombocytopenia via reduced platelet production after infecting the bone marrow in dengue-infected animal models	[33,51, 52]
	Complement-mediated platelets destruction	[56]
ZIKV	The immunemediated mechanisms of severe thrombocytopenia	[66]
	Causes hematological abnormalities	
CMV	Invading of megakaryocytes and their precursors by CMV throughout the acute phase of infections	[72]
	Viral antigens' ability to molecularly imitate host proteins	[70]
	The reticuloendothelial system clears more platelets as a result of immune dysregulation	[71]
	HCMV binds platelet receptor TLR2, triggering platelet-neutrophil attachment, neutrophil activation, and degranulation of HCMV-activated platelets	[73]
EBV	The infection results in an autoimmune reaction against the platelets, immune complexes, or antiplatelet antibodies	[66]
	Defective platelet generation	[66]
	Altered reticuloendothelial function, a virus-antivirus combination may exploit the reticuloendothelial system to persistently target and eliminate platelets.	[66]
	The identification of platelets by autoantibodies (Ig G, IgA, and IgM), which facilitates their phagocytosis by macrophages, mostly in the spleen	[78]
	Platelet lysis as a result of complement activation	[78]
	Autoimmune reactions to the virus might result in antibodies against platelet membrane glycoproteins	[79]
	The development of heterophile antibodies by naive B cells, the auto-reactive antibodies attach to platelets and destroy them	[33]
	Polyclonal antibodies made by latently infected B cells contain autoantibodies against platelets	[33]
Influenza virus	The degree of thrombocytopenia was correlated with the degree of inflammation measured by the serum C-reactive protein (CRP) concentration and elevated levels of lactate dehydrogenase (LDH) and serum transaminases	[83]
	Platelets express immune receptors such as CD40 and CD40 ligand (CD154), low-affinity type 2 receptor for the Fc portion of immunoglobulin G (FcgRIIA), and Toll-like receptors (TLRs). These immune receptors indicate the platelets' capacity to actively engage in immune responses	[85]
HIV	Immune complexes and the existence of anti-PLT and anti-HIV antibodies that cross-react with the PLT membrane	[92]
	Immune-mediated platelet destruction in the periphery and decreased bone marrow production	[93]
	Cross-Reactivity with Platelets, cross-reactivity between viral and platelet proteins can mistakenly trigger the immune system to attack both, causing peripheral platelet destruction	[93]
	Hepatitis Coinfection, coinfection with HCV and HBV and liver damage caused by these hepatitis viruses can reduce the production of thrombopoietin	[93]
	Direct HIV Infection, infecting megakaryocytes and platelets via CXCR4 receptors, disrupting their function and reducing platelet production	[94]
	Treatment-Related Thrombocytopenia, some medications can decrease bone marrow function	[94]
	IVIG also suppresses Fc receptors in the spleen and macrophages, restricting their platelet-destructive activity	[94]
SARS-CoV/SARS-CoV-2	Direct Infection of Hematopoietic Cells:	[97]
	• Viruses directly infecting hematopoietic stem cells and megakaryocytes	[97]
	• Interaction with specific receptors like CD13, CD66a, and ACE2 on these cells can inhibit their growth and induce apoptosis	[98] [100]
	• This interaction disrupts normal hematopoiesis	[100,101]
	Immune-Mediated Destruction, the patient's immune system becomes dysregulated and produces autoantibodies against glycoproteins on the surface of platelets	[97]
	Overactivated immune responses and cytokine storm, overproduced cytokines like GM-CSF and IL-6 can damage hematopoietic progenitor cells in the bone marrow and this damage disrupts the normal platelet production process	
	Lung damage induces aggregation of platelets and reduction of circulatory platelets	
Adenoviruses	Platelet Activation, adenoviruses can activate platelets by attaching to specific receptors on their surface. These receptors include integrins (such as vb3 or 5b1) and the Coxsackie and Adenovirus Receptor (CAR). Activation of platelets can lead to their removal from circulation, contributing to thrombocytopenia	[107] [111]
	Platelet-leukocyte aggregate formation	
Measles Virus	MMR Vaccination	[119]
	Natural Measles Infection, the virus itself can directly affect platelet counts	[116–118]
Parvovirus B19	Bone Marrow Suppression, B19 primarily reproduces within erythroblasts in the bone marrow, and the infection can interfere with normal bone marrow function	[122] [121]
	Immunologic Mechanisms	[122]

(*continued on next page*)

Table 1 (*continued*)

Virus	Mechanism	Reference
	Weakened Immune Systems	[122]
	Chronic inflammation	[122]
	Production of autoantibodies	[122]
	Molecular mimicry, the immune response may inadvertently target host cells, including platelets	

Platelet sequestration is observed in congestive splenomegaly resulting from portal hypertension. This condition can be associated with cardiac failure, hepatic vein thrombosis, vena cava thrombosis cirrhosis, and, in rare cases, arteriovenous malformation of the splenic vessels [24] (Table 1).

The hallmark of thrombotic microangiopathy (TMA) is the development of blood clots in small blood arteries. Platelets are essential for the production of TMA, and a variety of processes influence this process. The process of TMA often begins with endothelial injury, which makes the subendothelial matrix visible and activates platelets [25]. Platelet adhesion and aggregation are caused by deviations in the control of von Willebrand factor (vWF) and ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 [26].Moreover, platelets are activated by the complement cascade, and complement system dysregulation can lead to TMA [27]. Furthermore, cytokines and inflammation can stimulate platelets, which further aids in the development of TMA [28]. It is important to recognize that TMA is a complex condition whose pathophysiology involves the interaction of multiple variables.

3. Platelets and viral infection

Viral infections frequently result in thrombocytopenia, and viruses employ a range of unique techniques to reduce the amount of circulating platelets. Megakaryocyte infection by viruses, which can result in megakaryocyte apoptosis, diminished megakaryocyte maturation, and ploidy, or diminished expression of the thrombopoietin receptor, can cause a reduction in platelet output [29]. Viruses can however affect hematopoietic stem cells, which leads to a reduction in progenitor cells and the creation of megakaryocyte colony-forming units with poor growth potential as a result of disrupted cytokine production by the infected cells in the bone marrow [30,31]. The induction of interferon-alpha/beta (IFNα/β), which inhibits the formation of proplatelets, and the targeting and modulation of liver functions, crucial for the production of the megakaryocyte growth and development factor thrombopoietin, are two additional indirect mechanisms through which viruses can affect platelet production [32]. The promotion of platelet lysis, which takes place during viremia, is another way that viruses cause thrombocytopenia. Viruses can interact with platelets directly or via immunocomplexes including viral antigens and immunoglobulins G (IgGs) [23]. Platelet surface integrins and antiviral antigens frequently interact, providing an additional mechanism for virus-induced platelet destruction [33].

Platelets have the potency for internalizing and interacting with pathogens making them a suitable target for virus invasion through various mechanisms [34]. Due to the presence of viral pathogen receptors on platelets, these viruses can more easily interact directly with platelets. Thrombocytopenia is a result of these viral infections and platelet interaction through several receptors [35]. Direct contact among both platelets and viruses results in the fastest manner for platelets to be destroyed. The cytokine profile of the host and altered thrombopoietin (TPO) production in the liver are only two examples of how viruses might modify platelet production at different stages of development. The simian immunodeficiency virus (SIV) is an example of a number of these viruses since it causes an increase in tumor growth factor (TGF) β, which in turn causes TPO production [29]. Reduced platelet production is demonstrated in patients with dengue infections and SIV, which is caused by TGF-mediated down-regulation of TPO in SIV cases. Other examples of these viruses are human herpesvirus 6 (HHV6), which can hinder the development of TPO-inducible megakaryocytic colonies, and human herpesvirus 7 (HHV7), which affects the megakaryocytes' capacity to survive and differentiate [29]. Certain viruses, including the hepatitis C virus (HCV), directly prevent the generation of TPO by destroying liver tissue. Megakaryocyte formation is slowed by decreased TPO production, which also lowers platelet production [36].

Idiopathic thrombocytopenia is a condition that affects blood platelet counts rather than function. As most causes are related to antibodies against platelets, it is also known as ITP, low platelet counts may cause bleeding diathesis and purpura [37]. Isolated thrombocytopenia without additional causes is referred to as primary ITP. Any type of thrombocytopenia other than primary is referred to as secondary ITP, which includes systemic lupus erythematosus, infections, and lymphoproliferative diseases [38].

Additionally, it has been demonstrated that platelet survival is hampered by B-lymphocyte generation of antibodies against certain viruses. Platelet autoantibody-induced thrombocytopenia or ITP, is the term used to describe the condition when these antibodies, which typically target the surface glycoproteins of viruses, exhibit cross-reactivity with platelet surface integrins such as GPIIb/IIIa or GPIb-IX-V [39]. Hantavirus, CMV, varicella-zoster, HIV, herpes viruses, HCV, SARS, EBV, and CMV have all been associated with ITP [40].

Destruction and reduced platelet production lead to chronic immune thrombocytopenic purpura (CITP). It has been determined that CITP is either a primary autoimmune disorder (idiopathic thrombocytopenic purpura) [41]. Secondary CITP is related to autoimmune collagen vascular illnesses such as lymphoproliferative disorders. CITP is connected to several chronic infections as well. Although previous studies have demonstrated a strong relationship between HIV infection and CITP, recent studies have demonstrated HCV can be an even more common etiology of CITP [42].

Furthermore, viral hemorrhagic fevers (VHFs) constitute a collection of zoonotic diseases marked by fever and bleeding disorders, which may advance to shock and, in severe cases, result in death. These diseases are attributed to various RNA viruses [43,44]. VHFs are all accompanied by thrombocytopenia. VHF consists of the family of *Filoviruses* (Ebola and Marburg), *Arenaviruses* (Lassa and New

World arenaviruses), *Bunyaviruses* (Congo-Crimean Hemorrhagic Fever and Rift Valley Fever), and *Flaviviruses* (yellow fever) [45].

The geographical distribution of VHFs is constrained by the habitats of their natural hosts, with human beings serving as incidental hosts. Outbreaks of VHF occur sporadically, leading to these viruses consistently emerging or re-emerging in locations where optimal conditions are present. Dengue virus, along with Yellow fever (YF) virus, another flavivirus, ranks as one of the most globally distributed arthropod-borne diseases, holding the first and second positions, respectively [45].

The defining feature shared by all viral hemorrhagic fevers (VHFs) is a reduction in platelet numbers and/or function. This decline is typically accompanied by elevated levels of fibrinogen degradation products, prolonged prothrombin time (PT), and partial thromboplastin time (PTT). Additionally, at least five days after the onset of fever, a pronounced leucopenia and heightened viral loads are observed, often correlating with fatal outcomes. Another common occurrence is an increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzymes, primarily indicative of liver damage [45]. The crucial aspects of platelet behavior in response to infections and their intricate involvement in the immune response has been declared. It outlines that platelets undergo activation when exposed to microbial by-products, complement reactions, and specific receptors, directing them to infection or injury sites. At these sites, thrombin further activates platelets. Moreover, platelets' direct interaction with pathogens happens by recognizing them through Toll-like receptors (TLRs). This suggests a direct role for platelets in pathogen recognition and response. In terms of immune responses, the text underscores platelets' dynamic involvement beyond their traditional role in hemostasis. Platelets release various antimicrobial factors, such as platelet factor 4 (PF-4), RANTES, and others. Additionally, they participate in antibody-dependent cell cytotoxicity against microbial pathogens, emphasizing their active contribution to the innate immune response [46–48]. Interactions between platelets and VHFs remain inadequately understood, displaying distinct characteristics in each disease. However, certain mechanisms appear to be shared across all VHF pathogeneses [45].

Dengue virus (DENV), a member of the Flaviviridae family, stands as the most widespread arthropod-borne VHF.

4. Arboviruses

DENV poses a threat to further than half of the world people and is the most common arbovirus globally, expected to infect 100–400 million people each year [49]. The severe DENV infection is characterized by thrombocytopenia, and individuals with DENV infection have lower platelet counts than those with other febrile infections [50]. Dengue hemorrhagic fever (DHF) is uncommon because it usually results from a secondary infection, while the primary infection only causes mild flu-like symptoms. There are only four different DENV serotypes and infection with a second serotype causes dengue hemorrhagic fever. This implies that DHF cannot occur without the presence of anti-DENV antibodies, a phenomenon described as antibody-dependent enhancement (ADE). It has been demonstrated that these antibodies interact with Fc receptors to promote viral absorption and replication. Nonetheless, probably, antibody binding to DENV will also activate platelets in a way that is FcgRIIa-dependent. There is evidence that increased endothelial permeability results from this platelet activity. Infection of the bone marrow occurs in dengue-infected animal models, which may cause platelet production to be reduced and result in thrombocytopenia. Patients with dengue who are hospitalized usually develop severe thrombocytopenia, which is linked to extended hospitalization, the presence of clinically alarming signs, and plasma leakage [33,51,52]. The circulation of DENV particles and immunological factors generated during the acute phase of DENV infection can be directly linked to platelet activation [53,54]. Thrombocytopenia is brought on by activated platelets going through degranulation, attaching to the arterial wall, and forming thrombi, which effectively removes them from circulation [55]. The DENV NS1 protein binds to platelet-expressed TLRs 4 and 2, which activates the platelets, causes them to aggregate, attach to endothelial cells, and triggers macrophage phagocytosis [53]. In addition, complement-mediated platelet destruction plays an important role during dengue infection [56].

The Zika virus (ZIKV) was initially discovered in a rhesus macaque in the Zika jungle in Uganda in 1947 [57]. Later, serological tests on human serum samples in Uganda revealed the presence of virus-neutralizing antibodies, presenting the first proof that the virus may infect human [58,59]. The Americas experienced a significant ZIKV outbreak in 2015–2016, which increased the prevalence of congenital defects in infants as well as Guillain–Barré syndrome in adults [60]. A tiny percentage of ZIKV infections had platelet counts of less than 150×10^9/L, however severe thrombocytopenia, which is linked to bleeding, liver failure, and other coagulation problems, has been observed in fulminant cases [61,62]. Studies have shown that in DENV infections, thrombocytopenia manifests more frequently than in ZIKV infections, and it can be utilized to somewhat differentiate the two otherwise identical illnesses [63–65]. Multiple reports of patients with ZIKV virus infection who have clinical presentation consistent with ITP, support the immunemediated mechanisms of severe thrombocytopenia. It is infrequently observed that Zika virus infection causes hematological abnormalities. ITP and Evan's syndrome were confirmed by bone marrow biopsies (Reports of hypercellularity without dysplasia Before, there had been case studies of thrombocytopenia linked to Zika virus infection [66]. Blood smear results revealed macro platelets and significant platelet decreases, and one blood smear from a patient with non-severe thrombocytopenia was compatible with hemolytic anemia [67].

5. Cytomegalovirus (CMV)

A common virus that affects individuals all around the world is cytomegalovirus (CMV). Although it is well recognized that CMV may induce thrombocytopenia, this connection is likely underdiagnosed in healthy adults since CMV infection typically has no symptoms or very moderate symptoms [68]. Thrombocytopenia and CMV infection may be related, according to certain theories [69]. Among these relationships is the viral antigens' ability to molecularly imitate host proteins [70]. The reticuloendothelial system clears more platelets as a result of immune dysregulation [71]. There are two basic processes for how CMV-associated thrombocytopenia

develops: One involves the invasion of megakaryocytes and their precursors by CMV throughout the acute phase of infections [72], and the other involves immune-mediated thrombocytopenia that takes place throughout or after symptom clearance [69]. Although these theories have not yet been experimentally confirmed, conceptually, the latter is believed to react favorably to steroids and the former should gain from antiviral medications. As it might be challenging to discern between these two possibilities in clinical practice, secondary ITP has often been applied to CMV-associated thrombocytopenia [68]. The platelet receptor TLR2 is bound by the human cytomegalovirus (HCMV), which causes platelets to attach to neutrophils, which activates the neutrophils and causes degranulation of HCMV-activated platelets. Following this mechanism, a neutrophil-mediated immune response occurs [73]. In individuals with congenital CMV infection, thrombocytopenia often develops. Congenital CMV infection can be shown with the use of CMV DNA found in dried umbilical cords. Neonatal thrombocytopenia, which affects 1%–5% of healthy term newborns and 20%–50% of unwell infants, is rather frequent [74]. As CMV infection can occasionally produce severe, refractory thrombocytopenia that necessitates antiviral medication, it is important to investigate CMV in suspected instances of thrombocytopenia [75].

6. Epstein Barr virus (EBV)

Hematological abnormalities are frequently brought on by acute Epstein-Barr virus (EBV) infection, most notably atypical lymphocytosis [76]. Atypical lymphocytosis, which is a characteristic of infectious mononucleosis, is the primary hematological abnormality that is often brought on by EBV infection, and simple cases frequently present with minor declines in platelet counts [77]. Additionally, minor platelet count reductions are typical in simple situations; nevertheless, severe thrombocytopenia is quite uncommon [76].

A very uncommon side effect of acute Epstein-Barr virus (EBV) infection is severe thrombocytopenia [77]. However, the etiology is still not fully understood. According to research, viruses including the Epstein-Barr virus (EBV) can cause ITP in people. The cause of thrombocytopenia in viral illness appears to be multifaceted [66]. The most frequent explanations for thrombocytopenia-associated viral diseases involve possible immune system deterioration that may be brought on by immune complexes or antiplatelet antibodies, defective platelet generation, or altered reticuloendothelial function [66]. While microorganism infections can be transient and appear to be commonly unusual or naturally severe, these infections result in an autoimmune reaction against the platelets [66]. The reticuloendothelial system may be used by a virus-antivirus combination to continue attacking the surface of platelets, kill and eliminate them [66]. Also, the megakaryocytes in the bone marrow that promote the production of defective platelets might specifically result in a viral particle [66]. A little defect in the platelets may stimulate the development of the autoantibodies. The virus may inhibit T-cell activity, which would also inhibit cell-driven responses [66]. The identification of platelets by autoantibodies, which facilitates their phagocytosis by macrophages, mostly in the spleen, and their lysis as a result of complement activation are two mechanisms that contribute to the decline in platelet count in ITP [78].

Low platelet count, an autoimmune disorder (AID) known as ITP [78], is distinguished by the early mobilization of platelets that is brought on by the reticuloendothelial system after sensitization by antiplatelet glycoprotein autoantibodies [66]. Complement-mediated lysis, insufficient thrombopoiesis, or a viral infection that compromises the body's immune system are possible additional aspects of the illness [66]. The thrombocytopenia associated with acute EBV infection has been explained by several different mechanisms [79]. In around 40% of individuals, autoimmune reactions to the virus might result in antibodies against platelet membrane glycoproteins [79]. It was observed that infection of antibody-deficient mice does not cause thrombocytopenia, indicating that the antibody is the mediator of platelet depletion [80]. The development of heterophile antibodies by naive B cells that have been infected with latent-phase EBV is a hallmark of initial EBV infection [33]. Some of these antibodies might be auto-reactive and attach to platelets, destroying them [33]. It was discovered that thrombocytopenia depended on viral latency and was caused by antibodies elicited by the infection, confirming the idea that polyclonal antibodies made by latently infected B cells contain autoantibodies against platelets [33]. The auto-antibodies produced by other viral infections, which are thought to be the consequence of molecular mimicry between viral and self-antigens, are distinct from this process, which seems to be specific to EBV infection [33].

Although early infancy is the time of initial Epstein-Barr virus (EBV) infection, the majority of cases are often asymptomatic [81]. Fewer are linked to acute infectious mononucleosis (IM), which is characterized by liver failure, tonsillitis, lymphadenopathy, fever, and splenomegaly [81]. Although ITP is known to be brought on by the Epstein-Barr virus (EBV), little is known about how EBV manifests itself in spleen tissues [66].

Furthermore, ITP is brought on by an aberrant T cell response that prompts the growth and differentiation of autoreactive B cells in the spleen, phagocytose platelets [78]. As the primary antigen-presenting cell during ITP, macrophages help maintain the auto-immune response [78]. By promoting platelet death, $CD8^+$ T lymphocytes also contribute to thrombocytopenia [78]. Inappropriate bone marrow production further worsens thrombocytopenia because of an immunological reaction to megakaryocytes, in addition to this peripheral platelet destruction [78]. Moreover, during ITP, the amount of thrombopoietin, the primary growth factor of megakaryocytes, is low [78].

The majority of people become infected with EBV at a young age, similar to all other human herpesviruses [33]. This commonly results in infectious mononucleosis, a modest but occasionally prolonged viral symptomatic episode that is followed by lifelong latency [33]. Lifelong latency is created by human herpesviruses. Cancer, immune-proliferative diseases, transplantation issues, and thrombocytopenia can all result from viral recrudescence [80]. Thrombocytopenia and hemolytic anemia have been linked to the existence of platelet and erythrocyte autoantibodies in patients with primary EBV infection [33].

Autoimmune thrombocytopenia that develops secondary to other illnesses, usually infections, is referred to as second Harrington established in the 1950s that the administration of ITP patients' serum to healthy volunteers caused severe thrombocytopenia [78]. This was the first proof that a humoral factor—later identified as an IgG—was involved in the pathophysiology of ITP [78]. Other

antiplatelet antibodies (IgA and IgM) can also be found. However, they are typically seen in conjunction with IgG [78]. It should be noted that IgG has higher platelet phagocytosis than IgM.ary ITP [78].

7. Influenza virus

The Influenza virus belongs to the family *Orthomyxoviridae* and has a single-stranded segmented RNA genome [82]. According to the analyses, platelets with virus-containing vacuoles have been observed in an electron microscope, suggesting that the platelets had rapidly phagocytosed the viruses [83]. Regarding a retrospective study, from 21 patients with influenza infection (11 female) 9 (42, 95%) patients presented thrombocytopenia. In 4 of these 9 cases (44.4%) thrombocytopenia was accompanied by low mean platelet volume (under 7 fL) [83]. The degree of thrombocytopenia was moderate (96,000–11,0000/microL) and it was correlated with the degree of inflammation measured by the serum C-reactive protein (CRP) concentration [83]. Also, all these patients had elevated levels of lactate dehydrogenase (LDH) and serum transaminases [83].

Thrombocytopenia represents a commonly observed complication in the context of influenza virus infection, playing a significant role in predicting the clinical prognosis of critically ill patients. Nonetheless, a comprehensive understanding of the underlying etiological factors contributing to this phenomenon is currently lacking [84]. In addition to surface proteins responsible for recognizing damaged blood vessels and exposing the collagen matrix, platelets also express immune receptors such as CD40 and CD40 ligand (CD154), low-affinity type 2 receptor for the Fc portion of immunoglobulin G (FcgRIIA), and Toll-like receptors (TLRs). These immune receptors indicate the platelets' capacity to actively engage in immune responses [85]. Studies have also demonstrated that platelets play a crucial role as one of the initial cell types to reach an infection site. From there, they coordinate both innate and adaptive immune responses. This is achieved through the activation of immune cell recruitment, which involves neutrophils, macrophages, and $CD8^{+}$ T cells. Moreover, platelets are also capable of capturing bacterial pathogens, either directly or indirectly, by facilitating the creation of neutrophil extracellular traps [84]. Research reveals the presence of an early platelet-mediated innate immune response in the respiratory tract. This provides further insight into the mechanism of thrombocytopenia observed during influenza and other respiratory virus infections, which are linked to acute cardiovascular and thrombotic events [84]. Furthermore, thrombocytopenia has shown promise as a valuable marker for predicting in-hospital mortality in patients experiencing respiratory failure caused by H1N1 influenza in the intensive care unit setting [86].

8. Hepatitis C virus (HCV)

On a global scale, around 58 million individuals are currently affected by chronic hepatitis C virus infection, and approximately 1.5 million new infections emerge each year. Among these numbers, an estimated 3.2 million adolescents and children are living with chronic hepatitis C infection. According to the World Health Organization (WHO) assessment in 2019, the death toll attributed to hepatitis C reached approximately 290,000 individuals [87]. A notable percentage, ranging from 0.16% to 76%, of these patients experience accompanying thrombocytopenia [88]. Particularly, populations with a high prevalence of advanced cirrhosis have been observed to exhibit an increased occurrence of thrombocytopenia. Recognizing thrombocytopenia is of utmost importance due to its potential to amplify the risk of complications during invasive diagnostic or therapeutic procedures, necessitate interferon (IFN) treatment, and impact the management of patients awaiting orthotropic liver transplantation. Additionally, thrombocytopenia can serve as a significant risk factor for bleeding esophageal varices, impact chemotherapy for solid tumors or hematological malignancies, and influence surgical outcomes [36,89].

Thrombocytopenia can limit procedures, treatments, and increase bleeding risks [36]. For instance, patients with HCV who present with thrombocytopenia may face limitations in initiating antiviral treatment. In cases where treatment can be initiated, these patients might experience dose reductions or even discontinuation of therapy. Consequently, this can potentially lower their chances of achieving successful HCV treatment [90]. Thrombocytopenia can result from increased platelet destruction or decreased production. Proposed mechanisms include autoantibodies, hypersplenism, virus-induced bone marrow suppression, and reduced thrombopoietin production. Thrombocytopenia in hepatitis C is multifactorial, but understanding the mechanisms helps in treatment with drugs like eltrombopag [36]. Extensive research has explored the connection between autoimmune disease and thrombocytopenia in HCV. While autoantibodies may play a role in thrombocytopenia, there is insufficient evidence to support them as the primary cause in the majority of cases with chronic HCV infection [36].

Moreover, the hypothesis of viral-induced bone marrow suppression as a mechanism for thrombocytopenia development in chronic HCV patients has been proposed [36]. Furthermore, in response to an increased need for platelets, the body enhances the production and size of megakaryocytes. This process is regulated by TPO, a hematopoietic factor primarily synthesized in the liver. Although smaller quantities of TPO are found in the kidney, brain, and testes, it is not stored significantly but rather synthesized and promptly released. In cases of persistent thrombocytopenia, TPO levels experience exponential growth until reaching a stable state. The elevation of TPO levels occurs within 24 h following the onset of thrombocytopenia [91]. In the absence of platelets, there is minimal clearance of TPO by platelets, resulting in heightened TPO levels. This, in turn, stimulates bone marrow megakaryocytes and promotes increased Platelet production. The primary mechanism for TPO clearance involves its attachment to Platelets [91]. In general, the development of thrombocytopenia in chronic HCV patients is complex and involves multiple factors and aspects, which we mentioned some of them.

9. Human immunodeficiency virus (HIV)

The most prevalent subtype of HIV, known as HIV-1, is a member of the *Lentivirinae* subgroup of human retroviruses. It has nine distinct genes that encode structural proteins (gag and env) and regulatory elements (pol, vif, vpr, vpu, ver, tat, and nef) [92].

The envelope proteins gp120 and gp41 make up two of HIV's primary structural elements [92].

The primary high-affinity binding site for the HIV envelope protein gp120 is the cell surface antigen CD4, making cells expressing CD4 the virus's main target [92].

HIV also needs the coexpression of certain chemokine receptors, which means that the fusion of the virion to CD4 alone is not sufficient for cell entrance [92]. CXCR4 and CCR5 are the main co-receptors needed [92].HIV-1 T-cell tropic and M-cell tropic strains, which infect cells of the monocyte/macrophage and T lymphoid lineages, respectively, need CXCR4 and CCR5, respectively, for entrance [92].

One of the initial clinical symptoms of HIV infection is thrombocytopenia, which is seen in around 10–50% of HIV patients [92]. A focus has been placed on the rapid destruction of platelets (PLTs) brought on by immune complexes and the existence of anti-PLT and anti-HIV antibodies that cross-react with the PLT membrane among the several mechanisms proposed for HIV-related thrombocytopenia [92]. Moreover, co-infections or opportunistic infections, elevated viral load, and $CD4^+$ T lymphocyte counts of fewer than 200 cells per microliter all contribute to the incidence of thrombocytopenia and anemia [93].

HIV is a retrovirus that acts on cells that express CD4 protein in their cytoplasmic membrane to generate a multi-systemic illness [93]. However, AIDS is brought on by the gradual immunodeficiency brought on by a reduction in $CD4^+$ T cells after HIV infection, which makes a the primary consequences of HIV on the bone marrow, the site of hematopoiesis, including anemia and thrombocytopenia in the peripheral circulation of a person more susceptible to opportunistic infections and lowers their quality of life [93]. Increased thrombocytopenia is a side effect of HIV infection, and it may be brought on by both immune-mediated platelet destruction in the periphery and decreased bone marrow production [93].

The reasons for platelet alterations in PLWHA are diverse and might come from peripheral platelet destruction or reduced platelet generation. Due to the cross-reactivity between platelet glycoprotein IIIa and glycoprotein 120 in the viral envelope, peripheral damage often happens at the beginning of infection [93].

Idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura is caused by the cross-reactivity of this antibody, which encourages platelet capture and lysis in the reticuloendothelial system of the spleen or early apoptosis [93].

Several hematological symptoms, including anemia and thrombocytopenia, can be brought on by HIV infection. Due to the potential for liver damage, which lowers the synthesis of thrombopoietin [93]. Coinfection with the hepatitis C (HCV) and B (HBV) viruses can also cause thrombocytopenia in PLWHA [93]. Platelet count can predict the progression from asymptomatic HIV infection to AIDS since thrombocytopenia is the initial hematological indication of HIV infection and has a strong correlation with the onset of AIDS [93].

In 1982, thrombocytopenia in HIV patients was first identified. Increased illness and death, rapid CD4 count decline, and hastened development of full-blown AIDS are all linked to thrombocytopenia [94]. A recent study revealed that platelets can 'engulf' *Staphylococcus aureus* and HIV, which may be another factor contributing to thrombocytopenia's propensity for a faster illness progression [94].

A person's options for therapy are additionally constrained by severe thrombocytopenia because several medications decrease bone marrow and consume peripheral platelets [94].

Through the CXCR4 receptors, HIV may enter megakaryocytes and platelets. The virus begins to wreak havoc as soon as it enters the megakaryocyte [94].

In one study, the researchers discovered a threefold rise in megakaryocytes in HIV patients [94].

The lack of growth in mean platelet mass, however, indicates the existence of aberrant megakaryopoiesis [94]. The following causes contribute to thrombocytopenia in HIV patients:

Dysmegakaryopoiesis, or aberrant and dysfunctional generation of megakaryocytes and platelets, is caused by direct HIV infection of the megakaryocyte, which results in apoptosis and Peripheral platelet damage brought on by HIV cross-reactivity Abs [94].

In addition to having the propensity to shed epitopes, platelets are also capable of "donating" their CXCR4 receptors to CD4null and CXCR4null cells [94].

Both the P24 Ab and the anti-HIV gp120 Ab can and do cross-react with the GP111A receptor on the platelet [94]. Both HIV patients with and without idiopathic thrombocytopenic purpura (ITP) have shorter platelet life spans [94].

To defend the platelet, it appears that HIV induces $CD5^+$ cells to make IgM rheumatoid antibodies directed against the Fc component of IgG antibodies as well as Ab directed to the F(Ab)2 portion of the anti-GP111A Ab [94].

Early on in the HIV infection, peripheral destruction is the primary cause of thrombocytopenia, whereas later on in the advanced stage (AIDS), reduced production is more likely to be the cause [94].

In actuality, thrombocytopenia in CD4 counts 200 is linked with reduced platelet production while CD4 counts above 200 are associated with greater peripheral destruction [94].

Intravenous immunoglobulin raises platelet count, although it is expensive, time-consuming, and only used in chronic conditions [94].

Immunoglobulin dominates the immune system, and IVIG also suppresses Fc receptors in the spleen and macrophages, restricting their platelet-destructive activity [94]. A severe hemolytic condition known as thrombotic thrombocytopenic purpura causes red cell fragmentation, low platelet counts, and purpura [94]. The major pathophysiology is brought on by an ADAMTS-13 protease deficit or malfunction SO that This protease induces homeostasis by dissolving big molecules into smaller ones [94]. The platelet count is raised

by intravenous immunoglobulin, which is utilized in chronic instances but is expensive and time-consuming [94].

Immunoglobulins make up a large division of the immune system, and IVIG also inhibits Fc receptors in the spleen and macrophages, decreasing their ability to damage platelets [94].

10. Severe acute respiratory syndrome coronaviruses (SARS-CoV and SARS-CoV-2)

SARS-CoV and SARS-CoV-2 are members of beta-coronaviruses [95]. Hematological complications are common in COVID-19 patients and patients with SARS-CoV infection. Regarding a retrospective study involving 1099 patients from 31 provinces and direct-controlled municipalities in China, 36.2% of patients presented thrombocytopenia [96]. Also, platelet counts less than 150×10^9 10^{-1} was documented in 44.8% of the SARS-CoV patients of a hospital [96].

SARS-CoV can directly infect hematopoietic stem cells and megakaryocytes and cause growth inhibition and apoptosis through interaction with CD13 and CD66a receptors which results in abnormal hematopoiesis and thrombocytopenia. These receptors have been detected on platelets which can be directly triggered by SARS-CoV [97]. Furthermore, CD13 and CD-66a have been found to be potential targets for direct infection of hematopoietic stem cells in patients with SARS-CoV-2 infection [98]. Also, ACE 2 receptors on hematopoietic stem cells as an initial receptor for SARS-CoV and SARS-CoV-2 pathogenesis can be hypothesized as a potential target for a direct attack on hematopoietic stem cells [98].

One of the indirect mechanisms of thrombocytopenia in patients with SARS-CoV-2 infection is COVID-19-induced ITP [99]. These patients can manifest dysregulated immune responses and autoimmunity by producing autoantibodies against glycoproteins expressed on the platelet surface. It destroys platelets and thrombocytopenia in these patients [100]. This mechanism is hypothesized in patients with SARS-CoV infection as well as COVID-19 patients. In these patients, immune damage to blood cells occurs following the induction of autoantibodies and immune complexes [97].

Another indirect mechanism that contributes to the development of thrombocytopenia in patients with SARS-CoV-2 infection is over-activated immune responses and inflammatory cytokine storm which lead to the destruction of the hematopoietic progenitor cells in the bone marrow. In these patients, over-activated T cells overproduce granulocyte-macrophage colony-stimulating factor (GMCSF) and interleukin-6 (IL-6) which can be followed by immune damage to progenitor cells and disturbance of the production process of platelets and therefore, thrombocytopenia occurs [100,101].

Another indirect mechanism of thrombocytopenia in patients with SARS-CoV and SARS-CoV-2 infection is the overconsumption of platelets due to DIC as a complication of infection in these patients [97,102]. In these patients, DIC occurs due to activation of the vascular endothelium, platelets, and leukocytes. It leads to dysregulated thrombin generation which can be amplified by the inhibition of fibrinolysis and the impairment of natural anticoagulant mechanisms [103].

Another indirect mechanism of thrombocytopenia in patients with SARS-CoV and SARS-CoV-2 infection is the overconsumption and decreased production of platelets due to lung injuries as a pulmonary complication of an infection. In these patients, lung damage induces aggregation of platelets and thrombosis in injury sites which leads to overconsumption of platelets and reduction of circulatory platelets and subsequent thrombocytopenia [97]. On the other hand, lung injury following infection can cause effects on megakaryocytes and large cytoplasmic fragments which participate in platelet production in the pulmonary circulation. It leads to decreased production of platelets and thrombocytopenia in these patients [102].

Studies on patients with SARS-CoV-2 infection demonstrate that platelet surface P-selectin expression and circulating platelet-leukocyte aggregate formation increase during acute infection [104]. So, following increased platelet aggregation in these patients, the occurrence of thrombocytopenia is expected.

11. Other respiratory viruses (RV)

11.1. Adenoviruses (Adv)

Adenoviruses (Adv) seem to be the most researched in connection to platelets among viruses that cause minor upper respiratory tract infections. Adenoviruses employ the Coxsackie and Adenovirus Receptor (CAR) to bind to cells [33]. The CAR is expressed in practically all tissues, however, whether it is present in platelets is up for discussion [105]. Healthy human platelets have been shown to express this receptor but at extremely low levels (3.5%) [106]. Adenoviruses can activate platelets by attaching to integrins on the surface of the platelet, such as vb3 or 5b1, or the platelet coxsackie and adenovirus receptor [107]. After receiving adenovirus intravenously, acute thrombocytopenia has frequently been seen [108–110]. According to research, mice have thrombocytopenia between five and 24 h after receiving an adenovirus. The virus causes platelet activation and the production of platelet-leukocyte aggregates [111]. Human adenovirus 3 and 5 were incubated in platelet-rich plasma in in vitro experiments, and the results showed a moderate increase in platelet aggregation and platelet activation marker expression. Adenovirus 5 uptake by platelets was shown using Electron Microscopy [112,113]. Adenovirus-induced thrombocytopenia is a significant consequence of gene therapy methods that use this kind of vector. Knowing its mechanism might aid in the development of preventative strategies [111].

11.2. Measles virus (MV)

One of the most infectious viral infections in the world, measles causes feverish rash and can have significant consequences, including death [114]. The worldwide measles immunization program has been remarkably effective in lowering measles-related

sickness and mortality globally [115]. Thrombocytopenia may develop following a natural measles infection. Natural infection in humans has been the subject of studies published within the last ten years that frequently indicate moderate leukocytopenia and thrombocytopenia, usually with modest bleeding problems but without thromboembolisms [116–118]. A causal link between the MMR vaccination and thrombocytopenia has been demonstrated based on observational research, case reports, and biological plausibility [119]. According to significant US research, the MMR vaccine was shown to be responsible for 76% of immune thrombocytopenic purpura episodes among children aged 12–23 months in the six weeks following the immunization, and the study estimated

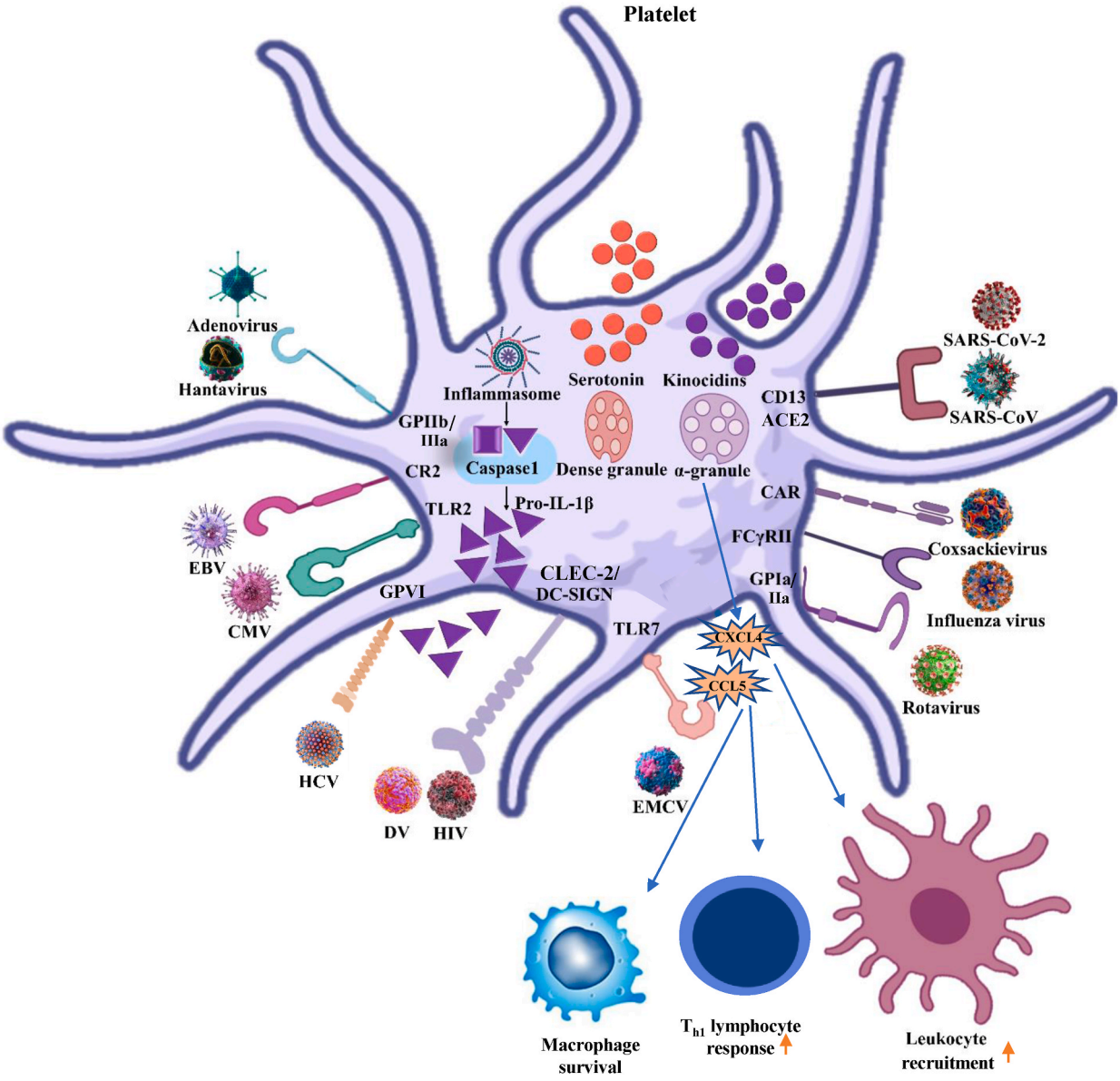

Fig. 1. The direct effects of viral infection on platelet destruction. The viral infection begins with the virus binding to susceptible cell receptors, and certain viruses can influence platelets by binding to specific receptors on their surface, thereby activating the platelets. Activated platelets release immune cytokines, triggering leukocytes for phagocytosis. Additionally, α-granules within activated platelets attract and activate phagocytes and lymphocytes, containing kinocidins that contribute to host defenses. Upon activation, platelets release α-granules rich in CXCL4, which upregulates coagulation and promotes leukocyte recruitment. CXCL4 also exhibits a dual role, reducing HIV infection while enhancing liver fibrosis. Another chemokine, CCL5, derived from α-granules, reduces HIV infection, boosts Th1 lymphocyte responses in HCV infection, and serves as a survival signal for macrophages during influenza infection. Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Encephalomyocarditis virus (EMCV), Human immunodeficiency viruses (HIV), Dengue virus (DV), Hepatitis C virus (HCV), Toll-like receptors (TLRs), Chimeric antigen receptors (CARs), Glycoprotein IIb/IIIa (GPIIb/IIIa), Complement receptor (CR), C-type lectin domain family 2 (CLEC-2), C–X–C chemokine receptor type 4 (CXCR4), chemokine (C–C motif) ligand (CCL), Dendritic cell-specific intercellular adhesion molecule-3-grapping non-integrin (DC-SIGN), Fc receptor γ II (FcγRII), Type 1 T helper (Th1).

that there is 1 case of ITP for every 40,000 vaccine doses administered [114]. Children with ITP who are vulnerable should receive the MMR vaccine at the suggested ages because MMR-associated ITP is uncommon, self-limiting, and not life-threatening. Vaccine-related thrombocytopenia was often moderate and went away on average within 7 days [120]. People with previous experiences of thrombocytopenia or thrombocytopenic purpura may be more susceptible to developing clinically severe thrombocytopenia after receiving the MMR vaccine; as such, a history of these illnesses should be taken into consideration before receiving the vaccine [114].

11.3. Parvo virus

The discovery of Parvovirus B19 (B19) occurred unexpectedly in 1974. Among the *Parvoviridae* family, B19 is the sole member recognized for causing disease in humans. This virus is widespread and the effects of infection differ based on the individual's immune and blood-related condition [121]. It mainly reproduces within erythroblasts in the bone marrow, and after an acute infection, B19 DNA has been observed to remain present in different body tissues for a person's lifetime. B19 infection typically leads to symptoms like erythema infectiosum, arthralgia, and fetal death [122]. Research on experimental B19 infection in humans has established a link between parvovirus B19 infection and thrombocytopenia [123]. Fulminant thrombocytopenia, a rare occurrence linked to B19 infection, can be categorized into two types. In the first type, thrombocytopenia occurs before the rash appears, caused by bone marrow suppression. The second type is likely influenced by immunologic mechanisms [121]. Thrombocytopenia associated with B19 can happen alone or alongside impacts on other blood cell types. This is more likely to occur during ongoing B19 infection and can affect both children and adults. The occurrence of thrombocytopenia during parvovirus B19 infection seems to be higher in individuals with weakened immune systems [122].

Several potential mechanisms have been suggested to explain the connection between B19 infection and thrombocytopenia, such as chronic inflammation, the production of autoantibodies, and a concept called molecular mimicry. Additional research is needed to comprehensively grasp the underlying causes of these relatively uncommon outcomes linked to B19 infection [122].

Direct effects of viral infection on platelet destruction are demonstrated in Fig. 1.

The different mechanisms that viruses use to cause thrombocytopenia are summarized in Table 1.

12. Conclusion

In conclusion, this manuscript has explored the intricate and multifaceted relationship between viruses and thrombocytopenia, shedding light on the diverse mechanisms through which various viral agents, including hepatitis C virus (HCV), measles virus, parvovirus B19, and others, contribute to platelet depletion. Our journey through the nexus of viruses and thrombocytopenia has revealed a complex interplay involving autoantibodies, direct viral-platelet interactions, and the tumultuous cytokine storms that ensue during viral infections.

In the end, our combined efforts have the potential to change the way that thrombocytopenia is managed, providing people who are impacted by this illness in the setting of viral infections with a better future.

13. Future perspective

Platelets are recognized for their capacity to adhere to diverse viral entities, a phenomenon posited as a potential underlying mechanism contributing to thrombocytopenia during infections [124]. The potential for new viral infections to cause thrombocytopenia is an ongoing concern. As new viruses emerge, researchers and healthcare professionals need to monitor their effects on various bodily systems, including the hematological system.

Vaccination represents the most economically efficient strategy for preventing and, in some cases, eradicating infectious diseases. Nonetheless, the occurrence of adverse reactions following vaccination is an inherent aspect of the process. Beyond the commonly observed vaccine-related adverse reactions, there have been documented instances of infrequent yet severe adverse reactions, such as secondary immune thrombocytopenia. Furthermore, the incidence of ITP linked to the MMR (Measles, Mumps, Rubella) vaccine is higher among children. Present data indicate that COVID-19 vaccines are also associated with thrombocytopenia as well [125]. The development and distribution of vaccines, especially in response to viral outbreaks, can also impact thrombocytopenia. There have been reports of rare cases of thrombocytopenia associated with certain vaccines. Monitoring and understanding these cases are crucial for public health. Furthermore, it is crucial to closely watch how new viral infections affect platelet counts and the occurrence of thrombocytopenia due to their ongoing emergence. This requires continuous research efforts. At the same time, finding potential treatments involves understanding how different viruses interact with platelet receptors and cause their breakdown. One way to address virus-induced thrombocytopenia is by developing antiviral drugs that stop viruses from attaching to and entering megakaryocytes and platelets. Another promising approach is to create synthetic platelet receptors that act as decoys, diverting viruses away from real platelets. An effective treatment method includes using immunotherapy to decrease inflammatory cytokine storms, which speed up platelet activation and clearance. Providing platelet transfusion support to severely thrombocytopenic individuals at risk of bleeding is a practical intervention. Additionally, using thrombopoietin receptor agonists that boost platelet formation and megakaryocyte development may help reduce thrombocytopenia.

Better understanding of relationship between viruses and platelets may reveal new ways to treat and prevent viral-induced thrombocytopenia. Ongoing research into mechanisms involving viral interactions with hematopoietic cells, antibody/molecular mimicry, and the exploration of immunomodulatory agents is essential. International collaboration and data sharing are vital to stay ahead of the evolving challenges posed by viral infections.

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CRediT authorship contribution statement

Reyhaneh Rasizadeh: Writing – review & editing, Writing – original draft, Data curation. **Fatemeh Ebrahimi:** Writing – original draft, Data curation. **Atefeh Zamani:** Writing – original draft, Data curation. **Amin Daei Sorkhabi:** Writing – original draft, Data curation. **Aila Sarkesh:** Writing – original draft, Data curation. **Javid Sadri Nahand:** Writing – review & editing. **Hossein Bannazadeh Baghi:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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