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Current knowledge of thrombocytopenia in sepsis and COVID-19

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Thrombocytopenia, characterized by a decrease in platelet count, is commonly observed in sepsis and COVID-19. In sepsis, thrombocytopenia can result from various mechanisms, including impaired platelet production in the bone marrow, accelerated platelet destruction due to increased inflammation, sequestration of platelets in the spleen, immune-mediated platelet destruction, or dysregulated host responses. Similarly, thrombocytopenia has been reported in COVID-19 patients, but the immune-related mechanisms underlying this association remain unclear. Notably, interventions targeting thrombocytopenia have shown potential for improving outcomes in both sepsis and COVID-19 patients. Understanding these mechanisms is crucial for developing effective treatments.

KEYWORDS

platelet count, sepsis, thrombocytopenia, COVID-19, platelet

1 Introduction

Thrombocytopenia refers to a condition characterized by abnormally low levels of blood platelets—a vital component of the body's clotting system. It can be triggered by various factors such as medications, infections, autoimmune diseases, and other health conditions (1). Thrombocytopenia can lead to symptoms like excessive bruising and bleeding and may result in severe complications such as an increased risk of stroke, heart attack, or death (1). Investigating the causes and exploring effective treatments for thrombocytopenia are essential for improving patient prognosis and quality of life.

Sepsis is a life-threatening condition characterized by excessive inflammation caused by infection. It has seen a significant increase in incidence—8.7% over recent decades—due to the body's exaggerated response to infections (2). Coagulation disorders play a major role in sepsis-related mortality ranging from mild thrombocytopenia to fatal conditions like disseminated intravascular coagulation (DIC) (3). Platelets are crucial in sepsis, and thrombocytopenia serves as both a prognostic marker and an independent predictor of worse outcomes (4, 5). Notably, thrombocytopenia during sepsis is associated with increased overall 30-day mortality (6). Furthermore, platelets have the potential to be

therapeutic targets and modulators of sepsis (7), highlighting the significance of understanding thrombocytopenia in sepsis.

In recent years, the COVID-19 pandemic has profoundly impacted healthcare systems and individuals' health. Extensive research has shown that SARS-CoV-2—the virus causing COVID-19—affects various tissues and organs beyond the respiratory system. Studies have revealed that SARS-CoV-2 can directly or indirectly affect blood cells such as hematopoietic stem cells, megakaryocytes, and platelets (8, 9). Approximately one-quarter of COVID-19 patients develop thrombocytopenia Ashwell-Morell receptor, particularly within the first week after admission (8, 9). Thrombocytopenia in ICU-admitted COVID-19 patients has been associated with a significantly worse prognosis for severe cases (10), and even patients with normal platelet count at admission but developing thrombocytopenia during ICU stay exhibited lower survival rates compared to those without thrombocytopenia (11). Despite these observations, the mechanisms underlying COVID-19-associated thrombocytopenia remain poorly understood.

Therefore, this review aims to summarize the current knowledge regarding thrombocytopenia in sepsis and its association with COVID-19.

2 Mechanisms of thrombocytopenia in sepsis

Several complex mechanisms contribute to thrombocytopenia during sepsis. Dysregulated host responses, interactions with platelet receptors and complexes, and immune-mediated thrombocytopenia are among the identified mechanisms (12–14). However, the precise mechanisms behind these phenomena require further elucidation. Understanding these mechanisms is crucial for developing appropriate treatment strategies (15, 16).

2.1 Dysregulated host response

Thrombocytopenia can exacerbate the disturbed host response observed in sepsis, as evidenced by animal models and functional data (17). Disease severity strongly influences host response biomarkers in sepsis (12, 18). Interleukin mediators play a role in the host response, with elevated plasma levels of IL-6, IL-8, and IL-10 indicating cytokine network activation. Additionally, vascular endothelial activation (elevated soluble E-selectin and soluble ICAM-1) and compromised vascular integrity are observed. Coagulation abnormalities—prolonged aPTT and PT, increased plasma D-dimer levels, decreased antithrombin and protein C levels—contribute to thrombocytopenia in sepsis (12, 17, 18).

2.2 The interaction between platelet receptors and complexes

Platelet-receptor glycoprotein Ibalpha (GpIbalpha), part of the GP Ib-IX-V complex, and plasma von Willebrand factor (VWF) proteins play a role in hemostasis and the process of platelet attachment to the vascular endothelium (19). In septic shock, platelet inhibition prevents clotting, preserves endothelial function, and reduces tissue damage, potentially leading to improved outcomes (20).

The Toll-like receptors (TLRs) of the innate immune system recognize molecules of microbial origin by interacting with their transmembrane domains (21). TLR2, TLR4, and TLR9 are expressed on the surface of platelets. During sepsis, TLRs are activated, with TLR4 being involved in endotoxemia by recognizing lipopolysaccharide (LPS) proteins. Furthermore, LPS-induced thrombocytopenia is reduced because the expression of TLR4 is significantly decreased in activated platelets (13, 14). Studies have shown that the increase in cGMP in an LPS-induced TLR knockout model is also mediated through the TLR4 pathway and inhibited by anti-TLR4 blocking antibodies. TLR4 interacts with LPS to promote platelet secretion and enhance platelet aggregation (22).

Matrix metalloproteinases (MMPs) are enzymes that modulate extracellular matrix recycling. MMP-2 is a platelet agonist, while MMP-9 is a platelet activation inhibitor (Figure 1). Limited evidence suggests that toll-like receptor 4 (TLR-4) formation and platelet-leukocyte aggregates (PLA) may be associated with the development of sepsis-associated thrombocytopenia. However, current studies have found no difference in levels of MMP-2, MMP-9, and TLR-4 between donors with non-thrombotic and thrombotic sepsis. PLA formation is also increased in patients with thrombocytopenia. MMP-9 in platelets was detected using flow cytometry, gelatin enzyme spectrometry, and ELISA (23). Platelet consumption into the plasma may be the cause of thrombocytopenia in septic shock. The expression of MMP-9 in platelets increases during septic shock, suggesting that MMP-9 could be a potential therapeutic target for thrombocytopenia in sepsis (23).

2.3 Immune-mediated thrombocytopenia

The mechanism of immune-mediated thrombocytopenia is complex and still under exploration. The classical explanation is that platelets bound to autoantibodies on their surfaces are destroyed in the spleen or liver through interaction with Fcγ receptors (24). Autoantibodies can mediate platelet destruction through complement activation or desialylation (25–27). Aged desialylated platelets are cleared by the liver Ashwell-Morell receptor (AMR) (28). Recent studies have shown that conditioning platelets with anti-GPIB antibodies activate platelets, leading to the translocation of neuraminidase-1 to the surface, which desialylated platelets for Fc-independent hepatic clearance via AMR in the liver (26) (Figure 2). Studies have demonstrated that abnormal T cells, including T-helper (Th) cell differentiation into Th1 and Th17 phenotypes and reduced regulatory T cells, contribute to varying degrees of platelet destruction (24). Additionally, CD8+ T cells, especially cytotoxic CD8+ T cells, cause thrombocytopenia through phagocytosis of splenic macrophages or dendritic cells. Activation of CD8+ T cells in the bone marrow can also lead to damage to megakaryocytes and

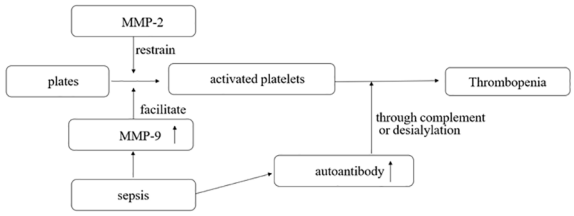

FIGURE 1
MMP-2 is a platelet agonist, and MMP-9 is a platelet activation inhibitor. In sepsis, the pathogen interacts with the body to produce a large number of antibodies, some of which can destroy activated platelets through complement or desialylation.

inhibit platelet production (24). Liver macrophages clear sialic acid-free platelets through macrophage galactolectin (29). Whether macrophage clearance of platelet aggregates affects antibody-induced hepatocellular-mediated platelet clearance remains unclear. Further research is still needed to understand the mechanism of immune-mediated thrombocytopenia.

It has been demonstrated that platelet levels of CD63 (LIMP-1), CD62P (P-selectin), and CD31 (platelet-endothelial cell adhesion molecule) are increased, while CD36 (GP IV) levels are significantly decreased during septic shock (30, 31). This suggests that platelet activation is mediated by interactions between platelets and leukocytes, endothelium, and activated endothelium, with platelet adhesion and aggregation being facilitated by these surface antigens (31).

Additionally, heparin-induced thrombocytopenia (HIT) is typically an immune-mediated thrombocytopenia (32) and is mediated by IgG antibodies that have specificity for platelet factor 4 antigen complexes (33). The consensus view is that these immune complexes activate platelets through Fc gamma RIIa receptors, leading to thrombocytopenia and thrombosis (34). Neutrophil extracellular traps (NETs) are complex structures composed of DNA and various proteins, including histones, neutrophil elastase, myeloperoxidase, and antimicrobial proteins. They have been increasingly reported in patients with infections and thrombosis associated with autoimmune and non-immune diseases (35, 36). When activated neutrophils release NETs, they form a mesh-like structure that traps and prevents platelets from binding to their receptors, resulting in thrombocytopenia. HIT immune complexes also activate neutrophils and induce the formation of NETs through MMP (33) (Figure 3).

Additionally, activated platelet/neutrophil interactions mediated by P-selectin and PSGL-1 also induce NETosis (37). Research has shown that neutropenia eliminates thrombosis. Conversely, neutrophil reconstitution restores thrombus deposition and leads to thrombocytopenia (33). Furthermore, NETs can activate the complement system (38), leading to the generation of anaphylatoxins that can directly lyse platelets and further contribute to the development of thrombocytopenia.

Moreover, studies have found elevated levels of platelet-related IgG in sepsis with thrombocytopenia. Anti-platelet autoantibodies (anti-GP IIb/IX) have also been detected in a small number of patients, such as idiopathic thrombocytopenic purpura, suggesting a potential immune-related process for thrombocytopenia in sepsis (15). In mouse models of immune thrombocytopenia (ITP), monoclonal antibodies IgG, which bind to cell surface-associated antigens, prevent the development of immune thrombocytopenia (39, 40). It has been suggested that phagocytosis of reticuloendothelial cells in the bone marrow may also cause thrombocytopenia (41).

2.4 Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) often occurs in patients with sepsis. It is mediated by pathogen-related molecules,

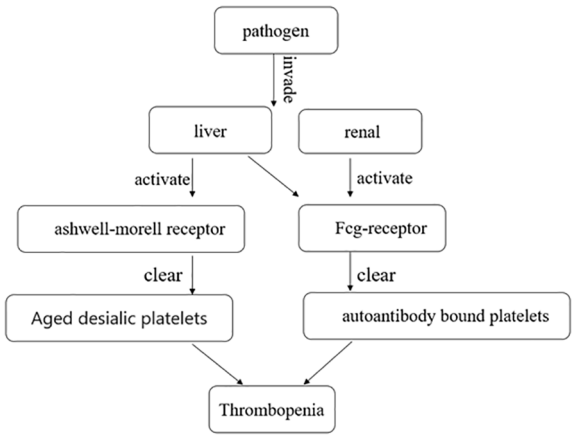

FIGURE 2
After the pathogen invades the liver and kidney, it clears aged desialic platelets and autoantibody-bound platelets by activating the Ashwell-Morell receptor and Fcg-receptor, respectively, causing thrombocytopenia.

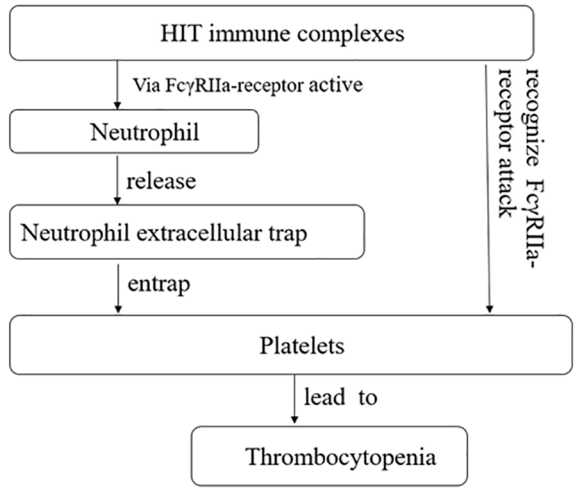

FIGURE 3
Heparin-induced thrombocytopenia (HIT) immune complexes via FcγRIIa-receptor active neutrophil, and further promotes the release of neutrophil extracellular trap, causing it to seize platelets, causing thrombocytopenia. HIT immune complexes attack plates through FcγRIIa-receptor, causing thrombocytopenia.

leading to upregulated expression of tissue factors and inhibition of anticoagulation and fibrinolysis mechanisms (42). Platelet activation and white blood cell involvement are widely reported (43). The underlying disease process, such as trauma-induced mechanical endothelial injury, sepsis-related inflammation, obstetric complications, or cancer, results in excessive release of tissue factor, leading to overproduction of thrombin. Thrombin increases its production by converting soluble fibrinogen into insoluble fibrin chains and activating other thrombin and factors. Thrombin activates platelets as a key component of the primary hemostatic mechanism through the TF/VIIa axis and the involvement of Factor XIIa. Additionally, complement-mediated responses can affect lytic cells and/or bacterial pathogens through the release of damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) and other cellular components that promote blood coagulation (3).

Once a fibrinolytic clot begins to form, the fibrinolytic cascade is activated to counteract increased fibrin deposition and aggregation in microvessels. However, this fibrinolytic activity is impaired by anti-fibrinolytic components such as thrombin-activated fibrinolytic inhibitors (TAFI), plasminogen activator inhibitors (PAI-1), and other prethrombotic mediators (44, 45). Similarly, damage to the physiological anticoagulant pathway, including tissue factor pathway inhibitors (TFPI), antithrombin (AT), and activated protein C (APC), fails to inhibit the progressive procoagulant state to some extent. Currently, there is a bidirectional cross-talk between abnormal coagulation and inflammatory mediators, where inflammation effectively induces the coagulation cascade while abnormal coagulation profoundly alters and perpetuates inflammation (46, 47). In sepsis, major pro-inflammatory factors include IL-1, IL-6, TNF-α, elastase, and cathepsin (48). Recent research has elucidated the role of other thrombogenic inflammatory response factors such as NETs, extracellular vesicles, and shedding of endothelial calyx (49). DIC involves various mechanisms, including endothelial dysfunction and vascular endothelial injury, initiation of the coagulation pathway, platelet aggregation, dysfunction of the anticoagulation system, impaired fibrinolysis, activation of the complement system, upregulation of the inflammatory response, and many other factors that contribute to thrombocytopenia. Furthermore, it is assumed that all patients with sepsis have certain disorders of coagulation and clot activation regardless of obvious symptoms of disseminated intravascular coagulation (DIC). Moreover, DIC also correlates with disease severity (50).

2.5 Increased destruction of platelets

There are specific diseases that, when they cause sepsis, are also accompanied by thrombocytopenia. The mechanisms underlying this increased platelet destruction are not well understood. One example is hemolytic uremic syndrome, a thrombotic microvascular disease primarily caused by endothelial cell injury, leading to a series of syndromes (51). These factors collectively contribute to peripheral thrombocytopenia (51). Additionally, there are articles describing other causes of thrombocytopenia in sepsis, such as hypersplenism, bone marrow failure, heparin-induced thrombocytopenia (HIT), drug-induced thrombocytopenia (DIT), and blood dilution (42, 52, 53). Further research is needed to elucidate the mechanisms underlying these specific diseases.

3 Mechanisms of thrombocytopenia in COVID-19

Based on previous studies, thrombocytopenia has been identified as one of the most common symptoms of COVID-19 (54). Furthermore, it has been observed that thrombocytopenia is associated with a threefold increased risk for severe COVID-19 and an elevated risk of mortality (55). Although the exact mechanisms of thrombocytopenia in COVID-19 are still being researched, several potential causes have been suggested. One prominent cause is the cytokine storm, which occurs when the immune system produces an excessive amount of cytokines that can destroy platelets and contribute to thrombocytopenia. Additionally, other causes include direct viral-induced cytopenias and immune-mediated destruction of platelets (56–58) (Figure 4).

3.1 Thrombocytopenia by affecting platelet production in COVID-19

Platelets are produced from megakaryocytes (MK), which derive from hematopoietic stem cells (59, 60). Hematopoietic tissue expresses ACE2 receptors, which are utilized by SARS-CoV-2 and SARS-CoV to invade host cells and tissues (61). CD34+ stem cells, platelets, and MK cell lines express CD13 and EACAM1a (CD66a) (62, 63). Studies have shown that SARS-CoV infects human MK progenitor cells and CD34+ cells (58), exhibiting similar antigenic characteristics to human HCoV-229E (64, 65). HCoV-229E enters monocytes and macrophages via CD13 and CEACAM1a (CD66a) receptors, inducing cell apoptosis (62, 66, 67). Therefore, CD13 and CD66a are potential receptors for viral entry. The interaction between viruses and host cells in the production of specific antibodies (68) can trigger autoimmune antibodies that lead to specific cell death. Consequently, SARS-CoV-2 infection may induce the production of autoantibodies and immune complexes or directly attack hematopoietic stem cells (HSCs) or hematopoietic progenitor cells, resulting in thrombocytopenia. For instance, individuals with thrombocytopenia infected with HIV-1 produce antibodies that cross-react with HIV-1 gp160/120 antigen, leading to increased levels of circulating immune complexes (69, 70). The immune system identifies and targets platelets packaged by antibodies and immune complexes via cells of the reticuloendothelial system, thereby attacking platelets. Hematopoietic cells expressing similar antigens are also vulnerable to damage (63). In summary, viral infections generate antibodies and immune complexes that are recognized by the body's immune system, causing thrombocytopenia by attacking blood-forming cells. Thus, it is plausible that SARS-CoV-2 might induce the production of autoantibodies and immune complexes or directly target HSCs or hematopoietic progenitor cells, ultimately resulting in thrombocytopenia.

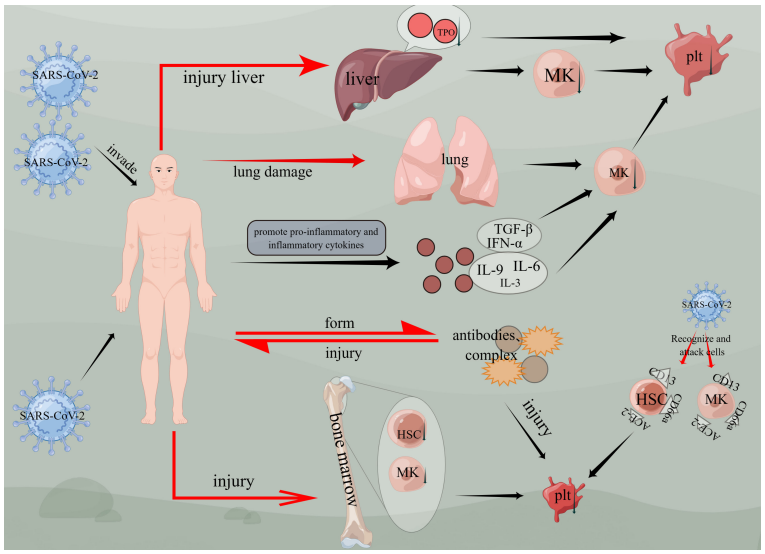

FIGURE 4
Mechanisms of thrombocytopenia caused by COVID-19. Viruses invade the body, cause liver and lung damage, and then damage megakaryocytes, causing thrombocytopenia. Viruses affect bone marrow hematopoietic function, affect hematopoietic stem cells and megakaryocyte generation, and cause thrombocytopenia. Thrombocytopenia is induced by CD13, ACE-2, and CD66a on hematopoietic stem cells or megakaryocytes. Inflammatory factors such as TGF-β, IFN-α, IL-3, IL-6, and IL-9 are activated, thus affecting the generation of megakaryocytes and the production of platelets. The virus enters the body and forms antibodies or compounds, and damages the body again. (figure by figdraw).

In addition, dysfunction of the local renin-angiotensin system can result in an abnormal bone marrow microenvironment (71, 72). SARS-CoV granules and inflammatory cytokines such as IL-1β and TNF-α promote ACE2 removal from the cell surface. This weakens ACE2 function, leading to renin-angiotensin system dysfunction and increased inflammation (68). Megakaryocytes are also present in the blood vessels of lung tissue, where they contribute to platelet release (73). When the virus attacks lung tissue, it damages lung epithelial cells and endothelial cells, causing vascular leakage and releasing large amounts of pro-inflammatory cytokines and chemokines (68). SARS patients often exhibit diffuse alveolar injury characterized by pulmonary tissue congestion, pulmonary edema, alveolar hyaline membrane formation, and fibrosis (62, 64). Extensive damage to the alveoli leads to the destruction of lung capillaries and subsequent lysis of megakaryocytes, resulting in thrombocytopenia (73, 74). Consequently, elevated levels of chemokines, inflammatory factors, growth factors, and anti-inflammatory factors affect the hematopoietic microenvironment. Moreover, an imbalance in the bone marrow microenvironment may impair thrombopoietin production as well as megakaryocyte differentiation and maturation to some extent, thereby contributing to thrombocytopenia.

3.2 Cytokine storm and immune system-mediated thrombocytopenia in COVID-19

During the COVID-19 pandemic, it has been observed that COVID-19 is a highly coagulant disorder associated with inflammation commonly seen in ICU settings. This phenomenon is often referred to as “thromboinflammation” and is linked to cytokine storms (75). In the case of COVID-19, the cytokines involved in cytokine storm mainly include tumor necrosis factor-alpha (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10), interferon alpha (IFN-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (56). When these cytokines are stimulated and activated, they cause inflammation, damage tissues, and lead to organ dysfunction. Additionally, many cytokines such as IL-3, IL-6, IL-9, IL-1, and stem cell factors can stimulate MK production (76–79). However, tumor growth factor-beta (TGF-β), platelet factor 4, and interferon-alpha (IFN-α) inhibit MK production (80). Elevated TGF-β levels have been observed in SARS patients. Plasma from active SARS patients inhibited the formation of MK colony-forming units, which could be neutralized by anti-TGF-β antibodies. This suggests that virus-induced TGF-β-mediated cytokine storms inhibit megakaryocyte generation, resulting in thrombocytopenia (58). IFN-α induces the production of cytokine signal transduction inhibitors that inhibit the expression of megakaryocyte-regulating transcription factors to some extent. This directly inhibits thrombopoietin (TPO)-mediated MK growth. Ultrastructural research supports this mechanism (81, 82), further indicating insufficient platelet production.

In summary, the specific mechanism of cytokine storm causing thrombocytopenia in COVID-19 is still being investigated. However, it is evident that when infected with COVID-19, a cytokine storm can lead to platelet disorders or thrombocytopenia by either directly destroying platelets or stimulating the production of antibodies that bind and destroy platelets.

Additionally, cases of thrombus formation with thrombocytopenia have been reported following administration of the AstraZeneca recombinant adenovirus vector vaccine (ChAdOx1 nCov-19) (83).

This phenomenon is referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS) (84). Studies have shown that some mechanisms of VITT are similar to those of heparin-induced thrombocytopenia (HIT), particularly involving platelet-activating anti-platelet factor 4 (anti-PF4) antibodies (85). Although pathogenic platelet-activating antibodies in VITT caused by vaccination are not common (86), it is important to actively explore the relevant mechanisms and implement effective prevention measures.

In conclusion, there are multiple mechanisms contributing to thrombocytopenia in critically ill patients and those infected with COVID-19, often involving a combination of several factors. It is crucial to consider different pathophysiological mechanisms when treating thrombocytopenia to effectively address the condition.

4 Treatments

4.1 Treatments of thrombocytopenia in sepsis

In the context of sepsis, several potential therapeutic targets have been identified for managing thrombocytopenia. Interleukin-11 (IL-11) has been shown to effectively prevent and treat chemotherapy-associated thrombocytopenia by increasing the production and differentiation of megakaryocytes. Studies have demonstrated that sepsis patients treated with IL-11 have a lower mortality rate (87). However, the use of IL-11 is limited due to serious side effects and is no longer used in clinical practice.

Another potential treatment option is recombinant human thrombopoietin, which has shown promising results in improving platelet counts more rapidly to normal levels and reducing the need for platelet transfusions in sepsis patients (88).

An animal study revealed that platelet granase B-mediated apoptosis occurs in the spleen and lung during sepsis. The progression of sepsis was found to be slowed down by inhibiting granase B using the platelet GPIIb/IIIa receptor inhibitor etibatitide both *in vitro* and *in vivo*. Inhibitors of GPIIb/IIIa receptors and other antiplatelet drugs delayed survival in mice with sepsis (89).

TAK-242, a compound that binds to TLR4 and inhibits lipopolysaccharide (LPS) activation, has shown potential as a toll-like receptor 4 (TLR4) inhibitor for treating immune factor-induced thrombocytopenia in sepsis (90, 91). Clinical studies using anti-TLR4 antibodies have demonstrated increased survival rates in mice with LPS endotoxemia (92). Additionally, TLR3, TLR5 antagonists, or TLR9 agonists have also improved survival rates in mice with LPS endotoxemia, suggesting their potential use in treating sepsis-associated thrombocytopenia (93, 94).

4.2 Treatments of thrombocytopenia in COVID-19

In the context of COVID-19, several treatment options have shown promise for managing thrombocytopenia. Tocilizumab (TCZ), a recombinant humanized monoclonal antibody against the interleukin-6 (IL-6) receptor, has demonstrated significant efficacy in treating cytokine release syndrome in COVID-19 patients. It binds to membranous IL-6R (mIL-6R) and soluble IL-6R (sIL-6R) (95). An Italian study reported that intravenous tocilizumab significantly improved the prognosis of ICU patients (96). Anakinra, an antagonist of IL-1R, has been suggested to block the secretion of IL-1β by macrophages, preventing tissue damage and inhibiting excessive platelet accumulation by blocking endothelial cell exposure and coagulation cascade propagation. Notably, patients treated with IL-1R inhibitors have shown better outcomes compared to those treated with IL-6R inhibitors (97).

Complement inhibitors have also shown potential for managing thrombocytopenia in COVID-19. Inhibition of the complement system can help inhibit abnormal activation of the complement cascade and thrombotic microangiopathies. Studies using eculizumab, a C5-blocking agent, demonstrated a rapid reduction in lactic acid levels, improvement in hypoxia, restoration of platelet counts, and improved prothrombin time (PT) within 15 days (98, 99). AMY-101 has been suggested as another complement inhibitor that follows a similar action to eculizumab in inhibiting hyperinflammatory states (100).

Inhibiting chemokines and chemokine receptors may contribute to the recovery of platelet numbers in COVID-19 patients. The anti-CCR5 antibody leronlimab has shown efficacy in reducing IL-6 levels, restoring T cell populations, reducing inflammatory responses, and indirectly mitigating virus-induced damage (101). Further exploration is needed to determine if leronlimab can effectively treat thrombocytopenia caused by COVID-19.

Thrombopoietin receptor agonists (TPO-RAs) are often used to treat COVID-19-related immune thrombocytopenias (ITPs). However, their use carries a risk of thrombosis (102, 103). Steroids, such as corticosteroids, have been used to treat COVID-19-related ITPs and have shown positive effects in reducing systemic inflammatory response and improving patient outcomes (104). A combination therapy using dexamethasone and intravenous immunoglobulin (IVIG) has demonstrated increased platelet counts within 12 hours after treatment and improved bleeding control and oxygenation in severe COVID-19 patients with ITP (105).

Recombinant human ACE2 (hrsACE2), which binds to viral spike proteins, has been explored as a therapeutic option for preventing tissue damage. Intravenous administration of hrsACE2 for seven days in severe COVID-19 patients has been shown to significantly reduce angiotensin II levels, inhibit IL-6 and IL-8-mediated inflammatory response, alleviate organ damage caused by SARS-CoV-2, and indirectly improve thrombocytopenia (106).

By targeting these receptors and utilizing specific drugs, it is possible to inhibit the process of thrombocytopenia in sepsis and COVID-19. Understanding these mechanisms can aid in the development of effective prevention strategies that improve outcomes for sepsis and COVID-19 patients.

5 Conclusion

Thrombocytopenia, characterized by low platelet count, is a common symptom observed in both sepsis and COVID-19 patients. The exact mechanisms underlying thrombocytopenia in these

conditions are still being researched, but several potential causes have been identified. In sepsis, cytokine storm plays a significant role in inducing thrombocytopenia. Excessive production of cytokines can directly destroy platelets or stimulate the production of antibodies that bind and destroy platelets. Therapeutic targets for managing sepsis-associated thrombocytopenia include IL-11 and recombinant human thrombopoietin, which have shown promising results in improving platelet counts. Additionally, inhibitors targeting TLR4 and GPIIb/IIIa receptors have demonstrated potential in animal studies. In this context, cytokine release syndrome contributes to thrombocytopenia. Drugs like tocilizumab (TCZ) and anakinra have shown efficacy in managing cytokine release syndrome by targeting IL-6 and IL-1 pathways. Complement inhibitors such as eculizumab have demonstrated positive outcomes in reducing inflammation and improving platelet counts. Chemokine inhibitors and thrombopoietin receptor agonists are also being explored as treatment options. However, it is important to maintain a balanced view when considering these treatments. Some therapeutic options come with limitations or risks. For example, IL-11 has serious side effects that restrict its clinical use, while TPO-RAs carry a risk of thrombosis. Furthermore, the effectiveness of certain drugs like leronlimab in treating thrombocytopenia caused by COVID-19 requires further investigation. And looking ahead, continued research is necessary to gain a comprehensive understanding of the mechanisms underlying thrombocytopenia in sepsis and COVID-19. This will enable the development of more targeted and effective treatments. It is crucial to consider the potential benefits and risks associated with each therapeutic approach, taking into account individual patient characteristics and disease severity. While progress has been made in identifying therapeutic targets for thrombocytopenia in sepsis and COVID-19, further research is needed to optimize treatment strategies. A critical evaluation of available options will help ensure that interventions are balanced, comprehensive, and tailored to the specific needs of patients. Prospective studies should focus on identifying biomarkers for early detection, elucidating the interplay between platelets and immune responses, and evaluating the efficacy of targeted therapies.

Author contributions

ML and HZ contributed to the conception and design of the study. HC, LF, CX, HH, and TT have conducted a literature review and analysis. JC wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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