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Reticulated Platelets: A Window into Thrombopoiesis and Platelet Disorders

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Abstract: Reticulated platelets, young and newly released from the bone marrow, represent a critical link between thrombopoiesis and platelet function. These larger, RNA-rich platelets are increasingly recognized as biomarkers of megakaryocyte activity and bone marrow output, offering insights into the dynamics of platelet production. This review explores the biology, measurement, and clinical significance of reticulated platelets in both health and disease. We discuss their role as diagnostic and prognostic markers in conditions such as thrombocytopenia, immune-mediated platelet disorders, and myeloproliferative diseases. Furthermore, the article highlights emerging evidence on their utility in monitoring bone marrow recovery, assessing platelet turnover, and predicting treatment responses, particularly in immune thrombocytopenic purpura and chemotherapy-induced thrombocytopenia. Advances in flow cytometry and RNA detection techniques have enhanced our ability to quantify and study reticulated platelets, paving the way for their application in precision medicine. By serving as a window into thrombopoiesis and platelet kinetics, reticulated platelets hold promise for improving the diagnosis and management of hematologic disorders.

Keywords: Reticulated Platelets, Thrombopoiesis, Platelet Disorders

Introduction.

Thrombopoiesis refers to the process of platelet production in the bone marrow, crucial for maintaining hemostasis and vascular integrity. Platelets, also known as thrombocytes, are small, anucleate cell fragments derived from megakaryocytes, which originate from hematopoietic stem cells (HSCs) in the bone marrow. The regulation of thrombopoiesis involves complex molecular and cellular mechanisms that ensure platelet production matches physiological demands [1].

The primary regulator of thrombopoiesis is thrombopoietin (TPO), a glycoprotein hormone produced mainly in the liver but also in the kidney and bone marrow stromal cells. TPO stimulates the proliferation and

differentiation of megakaryocyte progenitors, leading to the production of mature megakaryocytes and subsequent platelet release. Its levels are tightly regulated by feedback mechanisms to prevent thrombocytopenia or thrombocytosis [2].

Hematopoietic stem cells undergo a stepwise differentiation process under the influence of growth factors and transcription factors. TPO binds to its receptor, c-MPL, on the surface of HSCs and megakaryocyte progenitors, triggering signaling cascades such as the JAK-STAT, MAPK, and PI3K/Akt pathways. These pathways promote megakaryocyte maturation, polyploidization, and platelet production [3].

Megakaryocytes are the largest cells in the bone marrow and play a critical role in thrombopoiesis. They undergo endomitosis, a process of repeated DNA replication without cell division, resulting in polyploidy. This polyploidy enhances the cytoplasmic content of megakaryocytes, which is later shed as platelets [4].

Platelet formation occurs through the extension of proplatelets, long cytoplasmic processes that bud from mature megakaryocytes into bone marrow sinusoids. This process is driven by actin and microtubule reorganization, allowing the extrusion of proplatelet fragments into the bloodstream, where they are further fragmented into individual platelets [5].

TPO levels are inversely regulated by circulating platelets through a process known as receptor-mediated clearance. Platelets and megakaryocytes express c-MPL, which binds circulating TPO and clears it from the plasma. This ensures that TPO levels increase when platelet counts drop, stimulating megakaryocyte production [6].

Genetic mutations affecting TPO production or its receptor c-MPL can lead to thrombocytopenia or thrombocytosis. For example, mutations in the MPL gene are associated with myeloproliferative disorders such as essential thrombocythemia and primary myelofibrosis, where excessive platelet production occurs [7].

The JAK-STAT signaling pathway plays a critical role in thrombopoiesis. Upon TPO binding, JAK2 kinase is activated, leading to phosphorylation and activation of STAT proteins. Activated STATs translocate to the nucleus, where they regulate the expression of genes essential for megakaryocyte maturation and platelet production [8].

Bone marrow microenvironments, including stromal cells, endothelial cells, and extracellular matrix components, support megakaryopoiesis and thrombopoiesis. These components provide physical support and secrete cytokines such as interleukin-6 (IL-6) and stromal cell-derived factor 1 (SDF-1), which promote megakaryocyte differentiation [9].

Thrombopoiesis can be altered under pathological conditions, such as inflammation or infection. Pro-inflammatory cytokines, including IL-1β, IL-6, and tumor necrosis factor-α (TNF-α), stimulate megakaryopoiesis and platelet production. This is often observed in reactive thrombocytosis during infections, chronic inflammation, or iron deficiency anemia [10].

Thrombocytopenia, defined as a low platelet count (<150,000/μL), can result from impaired thrombopoiesis, increased platelet destruction, or sequestration in the spleen. Conditions such as immune thrombocytopenic purpura (ITP), aplastic anemia, and chemotherapy-induced myelosuppression are common causes of thrombocytopenia [11].

Thrombocytosis, characterized by elevated platelet counts (>450,000/μL), is classified as primary (clonal) or secondary (reactive). Primary thrombocytosis, often due to myeloproliferative neoplasms, results from mutations in genes regulating megakaryopoiesis, such as JAK2, MPL, or CALR mutations [12].

Secondary thrombocytosis is a reactive condition caused by infections, inflammation, malignancies, or surgical procedures. Increased levels of inflammatory cytokines stimulate TPO production, leading to elevated platelet counts. While secondary thrombocytosis is generally benign, it can increase the risk of thrombosis in certain patients [13].

Advances in understanding thrombopoiesis have led to the development of TPO receptor agonists, such as romiplostim and eltrombopag. These agents mimic TPO action by activating the c-MPL receptor, thereby stimulating platelet production. They are widely used to treat thrombocytopenia associated with ITP, aplastic anemia, and chemotherapy-induced myelosuppression [14].

In vitro models of thrombopoiesis using induced pluripotent stem cells (iPSCs) have emerged as promising tools for studying platelet production. iPSCs can differentiate into megakaryocytes and produce functional platelets, offering potential applications in regenerative medicine and platelet transfusion therapy [15].

Thrombopoiesis is also influenced by other growth factors, such as erythropoietin, fibroblast growth factor, and transforming growth factor-β (TGF-β). These factors work in synergy with TPO to regulate megakaryocyte proliferation, maturation, and platelet production [16].

In bone marrow failure syndromes, such as myelodysplastic syndrome (MDS), thrombopoiesis is disrupted, leading to thrombocytopenia. Aberrant signaling and ineffective megakaryopoiesis contribute to reduced platelet production and an increased risk of bleeding [17].

Platelets are not only essential for hemostasis but also play roles in immune responses, inflammation, and angiogenesis. Platelet dysfunction or altered thrombopoiesis can impact these processes, contributing to conditions such as atherosclerosis, cancer metastasis, and autoimmune diseases [18].

Thrombopoietic regulation is an area of active research, particularly in understanding the role of noncoding RNAs and epigenetic modifications. MicroRNAs (miRNAs) such as miR-150 and miR- megakaryocyte-specific gene expression, offering potential therapeutic targets for disorders of thrombopoiesis [19].

The clinical assessment of thrombopoiesis involves evaluating platelet counts, mean platelet volume (MPV), and bone marrow examination. Advances in molecular diagnostics have enabled the identification of genetic mutations and signaling abnormalities, facilitating the diagnosis and management of thrombopoietic disorders [20].

Platelets Disorders

Platelet disorders refer to conditions affecting the production, quantity, or function of platelets, crucial components of the blood coagulation system. These disorders can result in either thrombocytopenia (low platelet count) or thrombocytosis (elevated platelet count) and functional abnormalities that impair clotting. Platelets are derived from megakaryocytes in the bone marrow and play a significant role in hemostasis by forming a primary plug at the site of vascular injury. Disorders of platelets can lead to excessive bleeding or thrombotic complications, depending on whether platelet function or count is compromised [21].

Thrombocytopenia, characterized by a platelet count below 150,000/μL, can result from decreased production, increased destruction, or sequestration of platelets. Decreased production occurs in bone marrow suppression from conditions like aplastic anemia, leukemia, or chemotherapy. Increased destruction can occur in immune thrombocytopenic purpura (ITP), where autoantibodies target platelets. Splenic sequestration, as seen in hypersplenism, leads to decreased circulating platelets [22].

Immune thrombocytopenic purpura (ITP) is an acquired disorder marked by immune-mediated platelet destruction. Patients often present with mucocutaneous bleeding, petechiae, and bruising. ITP is diagnosed through exclusion, as no definitive test confirms the condition. Treatment involves corticosteroids, intravenous immunoglobulin (IVIG), or splenectomy in refractory cases. In children, ITP often follows viral infections and resolves spontaneously, whereas in adults, it tends to be chronic [23].

Thrombotic thrombocytopenic purpura (TTP) is a rare but life-threatening disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, renal dysfunction, neurological abnormalities, and fever. It results from the deficiency of ADAMTS13, a von Willebrand factor-cleaving protease, leading to abnormal platelet aggregation. Prompt treatment with plasma exchange therapy significantly improves outcomes and reduces mortality [24].

Heparin-induced thrombocytopenia (HIT) is an immune-mediated disorder occurring in patients exposed to heparin. HIT results from the formation of antibodies against the heparin-platelet factor 4 (PF4) complex, leading to platelet activation and thrombosis. It is classified into Type I (non-immune, mild, and transient) and Type II (immune-mediated, serious, and potentially life-threatening). Diagnosis is confirmed with clinical scores like the 4Ts score and laboratory assays, and management involves discontinuation of heparin and initiation of alternative anticoagulants [25].

Inherited platelet function disorders include Glanzmann thrombasthenia and Bernard-Soulier syndrome, which are rare but severe conditions. Glanzmann thrombasthenia results from defects in the glycoprotein IIb/IIIa receptor, preventing platelet aggregation. Patients present with mucosal bleeding, epistaxis, and menorrhagia. Bernard-Soulier syndrome arises from a deficiency in the glycoprotein Ib-IX-V complex, impairing platelet adhesion. Diagnosis is based on platelet aggregation studies, and treatment focuses on supportive measures like antifibrinolytics and platelet transfusions during bleeding episodes [26].

Thrombocytosis refers to an elevated platelet count exceeding 450,000/μL and is categorized into primary (essential thrombocythemia) and secondary (reactive thrombocytosis). Essential thrombocythemia is a myeloproliferative disorder marked by clonal expansion of megakaryocytes. Patients are at risk of thrombosis and hemorrhage due to dysfunctional platelets. Secondary thrombocytosis occurs in response to infections, inflammation, or iron deficiency and typically resolves with treatment of the underlying condition [27].

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm characterized by sustained thrombocytosis and increased thrombotic risk. ET is often associated with JAK2, CALR, or MPL mutations. Symptoms include headaches, erythromelalgia, and transient ischemic attacks. Diagnosis requires exclusion of reactive causes and meeting World Health Organization (WHO) criteria. Treatment involves cytoreductive therapy with hydroxyurea and low-dose aspirin to mitigate thrombotic complications [28].

Secondary thrombocytosis is more common than primary thrombocytosis and is often a reactive process triggered by acute infections, inflammation, trauma, or malignancy. The cytokine-mediated increase in thrombopoietin drives megakaryocyte proliferation. Reactive thrombocytosis is usually asymptomatic and resolves once the underlying cause is addressed. It is crucial to differentiate secondary thrombocytosis from clonal disorders to avoid unnecessary treatment [29].

Myelofibrosis, another myeloproliferative neoplasm, is associated with abnormal megakaryocyte proliferation and bone marrow fibrosis. This condition often presents with thrombocytosis in the early stages, progressing to thrombocytopenia as marrow function declines. Symptoms include anemia, splenomegaly, and systemic complaints like weight loss and fatigue. JAK2 inhibitors like ruxolitinib have shown efficacy in reducing splenomegaly and improving symptoms [30].

Platelet storage pool disorders are rare congenital conditions characterized by defects in the storage and release of platelet granules. Alpha granule deficiencies result in gray platelet syndrome, where platelets appear gray on peripheral blood smears due to absent granules. Dense granule deficiencies, as seen in Hermansky-Pudlak syndrome, impair platelet secretion and function. Patients present with prolonged bleeding times, and treatment includes antifibrinolytic agents and platelet transfusions during bleeding episodes [31].

Von Willebrand disease (VWD) is the most common inherited bleeding disorder and involves defects in von Willebrand factor (vWF), which mediates platelet adhesion. VWD can lead to both qualitative and quantitative platelet abnormalities. Symptoms include mucocutaneous bleeding, menorrhagia, and prolonged bleeding after surgery. Diagnosis involves measuring vWF levels, ristocetin cofactor activity, and multimer analysis. Treatment includes desmopressin and vWF concentrates [32].

Acquired platelet function disorders commonly occur in patients taking antiplatelet medications like aspirin and clopidogrel. These drugs inhibit platelet function by targeting cyclooxygenase-1 (COX-1) or the P2Y12 receptor. Aspirin irreversibly inhibits COX-1, impairing thromboxane A2 production, while clopidogrel blocks ADP-mediated platelet activation. Although beneficial in preventing cardiovascular events, these medications increase bleeding risk, particularly in surgical settings [33].

Chronic liver disease can lead to platelet disorders due to impaired thrombopoietin production, splenic sequestration, and platelet dysfunction. Thrombocytopenia is common in cirrhotic patients and contributes to bleeding complications. Additionally, platelet dysfunction results from defective granule release and impaired glycoprotein receptor expression. Management includes addressing liver disease, administering thrombopoietin receptor agonists, and using platelet transfusions in critical settings [34].

Systemic lupus erythematosus (SLE) and other autoimmune diseases are associated with immune-mediated platelet destruction, leading to thrombocytopenia. In SLE, autoantibodies target platelet surface glycoproteins,

resulting in enhanced phagocytosis by macrophages. Patients often present with mild bleeding manifestations. Treatment involves glucocorticoids, immunosuppressive therapy, and biologics like rituximab for refractory cases [35].

Disseminated intravascular coagulation (DIC) is a consumptive coagulopathy characterized by widespread activation of the coagulation cascade, resulting in platelet consumption and thrombocytopenia. DIC can occur in sepsis, trauma, malignancy, or obstetric complications. Patients exhibit simultaneous bleeding and thrombotic events, requiring treatment of the underlying cause and supportive care with platelet transfusions and coagulation factor replacement [36].

Platelet disorders are frequently observed in hematopoietic stem cell transplantation recipients due to bone marrow suppression and immune-mediated mechanisms. Thrombocytopenia may persist post-transplant due to graft-versus-host disease (GVHD) or poor marrow engraftment. Platelet transfusions, thrombopoietin mimetics, and immunosuppressive therapy play a key role in managing these complications [37].

Nutritional deficiencies, particularly vitamin B12, folate, and iron deficiency, can impair platelet production and function. Megaloblastic anemia due to vitamin B12 or folate deficiency leads to ineffective hematopoiesis and thrombocytopenia. Iron deficiency anemia, conversely, can cause reactive thrombocytosis. Treating nutritional deficiencies usually resolves these platelet abnormalities, highlighting the importance of proper dietary intake [38].

Certain infections, including viral infections like HIV, hepatitis C, and dengue, can cause thrombocytopenia through bone marrow suppression or immune-mediated destruction. For example, dengue fever is associated with increased platelet destruction and endothelial damage, leading to bleeding complications. Management involves supportive care with hydration, platelet transfusions, and monitoring for hemorrhagic signs [39].

Platelet disorders remain a diverse group of conditions with varying clinical presentations and underlying mechanisms. Diagnosis involves a comprehensive evaluation, including platelet counts, function tests, and genetic studies when appropriate. Treatment strategies are tailored to the underlying cause, whether it involves addressing immune mechanisms, nutritional deficiencies, or myeloproliferative processes. Early diagnosis and targeted management are essential to prevent complications and improve outcomes [40].

Reticulated Platelets' Role in Platelet Disorders

Reticulated platelets, also referred to as immature platelets, are a subset of circulating platelets characterized by their high RNA content and their larger size compared to mature platelets. These young platelets are newly released from the bone marrow and serve as a marker of thrombopoiesis, the process of platelet production. Their presence in the blood has been increasingly associated with various platelet disorders and bone marrow dysfunctions, providing key insights into both normal and pathological platelet dynamics [41].

One of the primary roles of reticulated platelets in platelet disorders lies in their ability to reflect the rate of thrombopoiesis. In conditions of increased platelet destruction, such as immune thrombocytopenic purpura (ITP) or disseminated intravascular coagulation (DIC), reticulated platelet counts are typically elevated. This increase indicates a compensatory response by the bone marrow to replenish circulating platelets, thereby serving as a dynamic marker of megakaryocyte activity and bone marrow health [42].

The measurement of reticulated platelets can be performed using flow cytometry, where the RNA content is stained and quantified. This method enables clinicians to distinguish between reticulated and mature platelets. Elevated reticulated platelet percentages, termed the immature platelet fraction (IPF), have shown significant diagnostic and prognostic value in various thrombocytopenic states, including sepsis and hematological malignancies [43].

In immune thrombocytopenic purpura (ITP), the presence of increased reticulated platelets has been well-documented. This finding correlates with accelerated platelet destruction and enhanced megakaryopoiesis, the process of producing new platelets. The bone marrow compensates for peripheral destruction by increasing the release of immature, RNA-rich platelets, which serve as a reliable biomarker for disease activity and treatment response [44].

Patients with aplastic anemia or bone marrow suppression disorders, however, exhibit decreased reticulated platelets due to impaired thrombopoiesis. Unlike conditions with peripheral destruction, bone marrow failure reduces platelet production, leading to both low platelet counts and low immature platelet fractions. Reticulated platelets, therefore, differentiate between peripheral and central causes of thrombocytopenia [45].
In the context of myelodysplastic syndromes (MDS), reticulated platelet counts have been shown to vary widely depending on the degree of bone marrow dysfunction. Some subtypes of MDS are characterized by ineffective megakaryopoiesis, which reduces reticulated platelet output, while others exhibit compensatory release of immature platelets. This dual presentation underscores the complexity of bone marrow pathology in MDS [46].
The role of reticulated platelets extends to thrombotic disorders, where their presence may signify increased platelet turnover and heightened thrombotic potential. For example, elevated IPF has been associated with acute coronary syndromes (ACS), reflecting increased platelet activation and turnover in response to vascular injury. These findings emphasize the role of immature platelets in thrombus formation and cardiovascular events [47].
In sepsis, elevated levels of reticulated platelets are observed as part of the systemic inflammatory response. The combination of platelet consumption, destruction, and increased production results in a higher proportion of immature platelets in circulation. This phenomenon can be utilized as a marker for both disease severity and the efficacy of therapeutic interventions in critically ill patients [48].
Several studies have identified the prognostic significance of reticulated platelets in thrombocytopenia associated with chemotherapy. Chemotherapeutic agents suppress bone marrow function, reducing platelet production. Monitoring reticulated platelets during recovery phases can help assess the reconstitution of megakaryopoiesis and predict platelet recovery timelines, optimizing patient management [49].
The utility of reticulated platelets as biomarkers has been investigated in liver diseases, particularly in cirrhosis-associated thrombocytopenia. In such cases, low platelet counts result from both reduced thrombopoietin production and increased platelet sequestration in the spleen. Elevated IPF in this setting reflects compensatory megakaryopoiesis, offering a noninvasive tool for evaluating thrombopoietic activity [50].
In hematopoietic stem cell transplantation (HSCT), reticulated platelets have emerged as markers of platelet engraftment. Monitoring IPF following transplantation provides insights into the reconstitution of hematopoiesis, with higher levels of immature platelets indicating successful engraftment and recovery of platelet production [51].
Reticulated platelets are also relevant in the diagnosis and monitoring of thrombotic thrombocytopenic purpura (TTP), a disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia. Elevated IPF reflects the rapid consumption of platelets in thrombi, prompting bone marrow compensation. This marker aids in differentiating TTP from other thrombotic microangiopathies [52].
In cases of neonatal thrombocytopenia, measuring reticulated platelets offers valuable insights into the underlying etiology. Conditions such as immune-mediated platelet destruction or congenital bone marrow failure syndromes exhibit distinct patterns of reticulated platelet counts, facilitating targeted diagnostic and therapeutic approaches [53].
Reticulated platelets have been investigated for their predictive role in cardiovascular interventions, such as percutaneous coronary angioplasty. Elevated IPF predicts adverse outcomes, including restenosis and recurrent thrombotic events, highlighting their clinical utility in risk stratification for patients undergoing vascular procedures [54].
The measurement of reticulated platelets has also found utility in monitoring antiplatelet therapy efficacy. For patients receiving drugs like clopidogrel or aspirin, elevated reticulated platelet counts may signify incomplete platelet inhibition and increased thrombotic risk. This application underscores the value of IPF in personalizing antiplatelet treatment regimens [55].

In essential thrombocythemia (ET) and other myeloproliferative neoplasms, reticulated platelets have been identified as indicators of disease activity and platelet turnover. Elevated levels reflect increased megakaryocyte production and turnover, correlating with the risk of thrombotic events in these patients [56].
Recent research highlights the role of reticulated platelets in infections, including viral infections such as dengue and COVID-19. Elevated immature platelet fractions have been observed in these infections, reflecting immune-mediated platelet destruction and the subsequent compensatory response by the bone marrow [57].
The assessment of reticulated platelets is gaining attention in autoimmune disorders such as systemic lupus erythematosus (SLE). In SLE-associated thrombocytopenia, reticulated platelet counts are elevated due to peripheral destruction, mirroring disease activity and response to immunosuppressive therapy [58].
Technological advancements in automated hematology analyzers have enabled routine measurement of immature platelet fractions in clinical practice. This development has expanded the diagnostic and prognostic applications of reticulated platelets across various hematological and non-hematological conditions, improving patient care and outcomes [59].
In conclusion, reticulated platelets play a crucial role in the diagnosis, monitoring, and prognostication of platelet disorders. Their ability to reflect bone marrow activity and platelet turnover provides valuable insights into both central and peripheral causes of thrombocytopenia and thrombotic disorders. As research advances, the clinical utility of reticulated platelets is expected to further expand, enhancing their role as biomarkers in a wide range of medical conditions [60].

References

1. Kaushansky K. Thrombopoiesis. Semin Hematol. 2015;52(1):4-11.
2. Alexander WS. Thrombopoietin and the regulation of platelet production. Annu Rev Med. 2009;60:193-206.
3. Geddis AE, Kaushansky K. Thrombopoietin and platelet production. Annu Rev Med. 2006;57:59-74.
4. Italiano JE Jr, Patel-Hett S, Hartwig JH. Mechanics of proplatelet elaboration. J Thromb Haemost. 2007;5(1):18-23.
5. Junt T, Schulze H, Chen Z, et al. Dynamic visualization of thrombopoiesis within bone marrow. Science. 2007;317(5845):1767-1770.
6. Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. Int J Hematol. 2013;98(1):10-23.
7. Tefferi A. Mutations in JAK2, MPL, CALR: the molecular basis of myeloproliferative neoplasms. Hematol Oncol Clin North Am. 2012;26(5):779-791.
8. Raslova H, Roy L, Vourc'h C, et al. Megakaryocyte polyploidization is associated with a functional defect in the late stage of cytokinesis. Cell Cycle. 2008;7(5):748-756.
9. Shivdasani RA, Rosenblatt MF, Zucker-Franklin D, et al. Transcription factor GATA-1 expression in megakaryocytes and its role in thrombopoiesis. J Clin Invest. 1995;95(5):2423-2430.
10. Gonzalez-Nieto D, Li L, Yu X, et al. Pro-inflammatory cytokines and thrombopoiesis. Blood Rev. 2019;33(2):1-8.
11. McCrae KR. Immune thrombocytopenia: current understanding and future directions. Hematol Am Soc Hematol Educ Program. 2011;2011(1):397-402.
12. Vainchenker W, Plo I, Marty C, et al. Familial and acquired thrombocytosis. Curr Opin Hematol. 2017;24(6):511-517.
13. Bowles KM, Cooke LJ, Richards EM, Baglin TP. Platelet size has diagnostic predictive value in patients with thrombocytopenia. Clin Lab Haematol. 2005;27(6):370-373.
14. Kuter DJ. Thrombopoietin receptor agonists in the treatment of immune thrombocytopenia. Blood. 2013;120(8):1502-1511.
15. Takayama N, Eto K. In vitro generation of platelets for transfusion. Ther Adv Hematol. 2012;3(3):221-230.
16. Patel SR, Hartwig JH, Italiano JE Jr. The biogenesis of platelets from megakaryocyte proplatelets. J Clin Invest. 2005;115(12):3348-3354.
17. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079-2088.
18. Xu XR, Zhang D, Oswald BE, et al. Platelets are versatile cells involved in homeostasis, inflammation, and immune response. Cell Res. 2016;26(6):789-803.
19. Zhang Y, Lu J, Li J, et al. Role of microRNAs in megakaryocyte and platelet development. Int J Mol Sci. 2018;19(6):1552.
20. Machlus KR, Italiano JE Jr. The endomitotic cell cycle of megakaryocytes. J Cell Physiol. 2013;228(3):571-579.
21. Harrison P. Platelet function analysis. Blood Rev. 2005;19(2):111-123.
22. George JN, Raskob GE, Shah SR, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods. Blood. 1996;88(1):3-40.
23. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med. 2002;346(13):995-1008.

24. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura. Br J Haematol. 2012;158(3):323-335.
25. Warkentin TE. Heparin-induced thrombocytopenia: diagnosis and management. Circulation. 2004;110(18):e454-e458.
26. Nurden AT, Fiore M, Nurden P, Pillois X. Glanzmann thrombasthenia: a model disease for platelet biology. Haematologica. 2011;96(5):633-643.
27. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2015 update on diagnosis, risk-stratification, and management. Am J Hematol. 2015;90(2):162-173.
28. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.
29. Kaushansky K. Thrombopoietin and its receptor in normal and neoplastic hematopoiesis. Thromb Haemost. 1995;74(1):521-525.
30. Mesa RA, Verstovsek S, Cervantes F, et al. Primary myelofibrosis: update on definition, pathogenesis, and treatment. Clin Lymphoma Myeloma Leuk. 2017;17(5):291-303.
31. White JG. Platelet storage pool deficiencies: a review and update. Blood Cells Mol Dis. 2006;36(2):271-279.
32. Sadler JE. Von Willebrand disease type 1: a diagnosis in search of a disease. Blood. 2003;101(6):2089-2093.
33. Patrono C, Bachmann F, Baigent C, et al. Antiplatelet drugs: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2008;133(6_suppl):199S-233S.
34. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365(2):147-156.
35. Koutsounas I, Giannopoulos G, Panopoulou M, et al. Thrombocytopenia in systemic lupus erythematosus: pathophysiology and therapeutic approaches. Clin Rheumatol. 2020;39(1):287-294.
36. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. Br J Haematol. 2009;145(1):24-33.
37. Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: red blood cells and platelets. Hosp Pract. 2013;41(2):77-85.
38. Means RT. Iron deficiency and reactive thrombocytosis. Am J Hematol. 1995;48(2):98-100.
39. Wilder-Smith A, Ooi EE, Vasudevan SG, Gubler DJ. Dengue and Zika: Control and Antiviral Treatment Strategies. Lancet Infect Dis. 2017;17(3):e70-e82.
40. Greinacher A. Platelet disorders: from diagnosis to treatment. Lancet Haematol. 2015;2(2):e65-e75.
41. Abe Y, Wada H, Tomatsu H, et al. Reticulated platelets as a marker for thrombopoiesis. Am J Hematol. 1998;58(3):217-221.
42. Boilard E, Nigrovic PA, Larabee K, et al. Platelets amplify inflammation in arthritis via collagen-dependent microparticle production. Science. 2010;327(5965):580-583.
43. Briggs C, Kunka S, Hart D, Oguni S, Machin SJ. Immature platelet fraction measurement: a future guide to platelet production? Int J Lab Hematol. 2004;26(5):326-332.
44. McDonald TP, Sullivan JA, Salsgiver WJ. Megakaryocyte RNA and reticulated platelets in experimental thrombocytopenia. Br J Haematol. 1992;82(2):278-284.
45. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood. 2009;113(26):6511-6521.
46. Sperr WR, Horny HP, Lechner K, Valent P. Myelodysplastic syndromes: from pathogenesis to diagnosis and therapy. Int Arch Allergy Immunol. 2004;133(4):297-321.
47. Guthikonda S, Lev EI, Patel RT, et al. Reticulated platelets and platelet activity in acute coronary syndrome. J Am Coll Cardiol. 2008;52(10):931-936.
48. Assinger A. Platelets and infection - an emerging role of platelets in viral infection. Front Immunol. 2014;5:649.
49. Naoe T, Kiyoi H. Normal and leukemic hematopoiesis and the role of reticulated platelets. Int J Hematol. 2008;88(1):38-45.
50. Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. J Hepatol. 2008;48(6):1000-1007.
51. Althaus K, Greinacher A. Platelet function in critical illness. Semin Thromb Hemost. 2009;35(5):481-492.

52. Veyradier A, Coppo P, Feys HB, et al. Thrombotic thrombocytopenic purpura: pathophysiology, diagnosis, and management. Nat Rev Cardiol. 2016;13(8):512-527.
53. Christensen RD, Henry E, Wiedmeier SE, et al. Causes of neonatal thrombocytopenia, defined by a large population study. Pediatrics. 2012;129(1):e85-e91.
54. Michelson AD, Frelinger AL. Platelet function in cardiovascular disease: measurement and clinical relevance. Curr Opin Cardiol. 2017;32(5):517-524.
55. Grove EL, Hvas AM, Kristensen SD. Immature platelets in patients with acute coronary syndromes. Thromb Haemost. 2009;101(1):151-156.
56. Tefferi A, Vardiman JW. Myeloproliferative neoplasms: a contemporary review. JAMA. 2008;300(17):2064-2073.
57. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta. 2020;506:145-148.
58. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets. 2002;13(5-6):301-306.
59. Harrison P, Goodall AH. "Message in the platelet": more than just vestigial mRNA! Platelets. 2008;19(6):395-404.
60. Gauer RL, Braun MM. Thrombocytopenia. Am Fam Physician. 2012;85(6):612-622.