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Coagulopathy in Thalassemia: Mechanisms, Risks and Clinical Consequences

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Abstract

Thalassemia, a group of inherited hemoglobin disorders, is traditionally associated with chronic anemia and iron overload. However, growing evidence highlights the significant role of coagulopathy in the clinical course of thalassemia, particularly in β -thalassemia intermedia and non-transfusion-dependent thalassemia (NTDT). This prothrombotic state is the result of a complex interplay between chronic hemolysis, abnormal erythrocyte membranes, platelet activation, and endothelial dysfunction. Together, these factors promote a hypercoagulable environment that places patients at risk of life-threatening thromboembolic events. Multiple contributors underlie the hypercoagulability observed in thalassemia patients. Hemolysis exposes phosphatidylserine on erythrocyte surfaces, iron overload induces oxidative stress damaging vascular endothelium, and splenectomy further exacerbates platelet activation and abnormal cell circulation. Moreover, deficiencies in natural anticoagulants, elevated procoagulant microparticles, and increased thrombin generation have been documented. These pathophysiological changes result in a heightened incidence of venous thromboembolism, pulmonary hypertension, and cerebrovascular complications, particularly in adults and splenectomized individuals. Early recognition and risk stratification are vital for preventing thrombotic events in thalassemia. Management strategies include careful transfusion regimens to suppress ineffective erythropoiesis, aggressive iron chelation to reduce oxidative injury, and the judicious use of antiplatelet or

anticoagulant therapy in high-risk patients. As research continues to unravel the molecular drivers of coagulopathy in thalassemia, integrating hematologic and vascular management may offer improved outcomes and quality of life for affected individuals.

Keywords: *Thalassemia, Coagulopathy, Hypercoagulability, Iron Overload, Thromboembolic Events*

Introduction

Thalassemia refers to a group of inherited hemoglobinopathies caused by mutations affecting the synthesis of alpha or beta globin chains, leading to ineffective erythropoiesis and varying degrees of anemia. Depending on the genetic mutations and clinical severity, thalassemia is classified into major, intermedia, and minor forms. While transfusion-dependent thalassemia (TDT), particularly β -thalassemia major, is characterized by severe anemia requiring lifelong blood transfusions, non-transfusion-dependent thalassemia (NTDT), such as β -thalassemia intermedia, displays a milder phenotype that still results in significant long-term complications [1-2]. Historically, the clinical management of thalassemia has focused on the hematologic manifestations—specifically anemia, hemolysis, and iron overload. However, accumulating evidence over the past two decades has drawn attention to a less visible but equally important complication: coagulopathy. Coagulopathy in thalassemia represents a hypercoagulable state that predisposes patients to both venous and arterial thromboembolic events (TEEs), significantly impacting morbidity and mortality [3-4].

The pathogenesis of coagulopathy in thalassemia is multifactorial. It includes chronic intravascular hemolysis, platelet activation, endothelial dysfunction, and abnormalities in coagulation and fibrinolytic pathways. Hemolysis leads to the exposure of negatively charged phosphatidylserine on the surface of red blood cells and circulating microparticles, which provide a catalytic surface for coagulation complexes. Additionally, the free hemoglobin released from lysed red cells scavenges nitric

oxide (NO), resulting in vasoconstriction, platelet aggregation, and endothelial activation [5-6]. One of the major risk enhancers of thrombotic events in thalassemia is splenectomy. The spleen plays a crucial role in filtering out damaged red blood cells and platelets. Following splenectomy, there is a marked increase in circulating procoagulant red cells and platelets, as well as platelet-derived microparticles, all contributing to a hypercoagulable state. NTDT patients, who are often splenectomized and not regularly transfused, are particularly susceptible to thrombotic complications [7].

Iron overload further contributes to coagulopathy in thalassemia through the generation of reactive oxygen species (ROS), which damage endothelial cells and disrupt normal vascular homeostasis. The accumulation of non-transferrin-bound iron (NTBI) and labile plasma iron (LPI) promotes oxidative stress, inflammation, and vascular dysfunction, which collectively prime the vasculature for thrombus formation. This effect is more pronounced in patients with inadequate iron chelation therapy [8-9]. Moreover, abnormalities in coagulation proteins, including elevated levels of procoagulant factors and reduced levels of natural anticoagulants such as protein C, protein S, and antithrombin III, have been observed in thalassemia patients. These changes tilt the hemostatic balance toward thrombosis. Elevated levels of D-dimer, thrombin-antithrombin complexes, and prothrombin fragments in asymptomatic patients suggest chronic, low-grade activation of the coagulation cascade [10-11].

Aim

This review aims to provide a comprehensive overview of coagulopathy in thalassemia by

elucidating the underlying pathophysiological mechanisms, identifying key risk factors, and highlighting the clinical consequences associated with thrombotic complications. Additionally, it seeks to inform clinicians and researchers about current strategies for diagnosis, prevention, and management of coagulopathy in both transfusion-dependent and non-transfusion-dependent thalassemia patients.

Methods

This narrative review was conducted to synthesize existing evidence on the mechanisms, risks, and clinical consequences of coagulopathy in thalassemia. A comprehensive literature search was performed using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Articles published in English from inception to June 2024 were considered. Search terms were combined using Boolean operators and included keywords such as “thalassemia,” “hypercoagulability,” “coagulopathy,” “thrombosis,” “venous thromboembolism,” “endothelial dysfunction,” and “platelet activation.”

Eligible studies included original research articles, systematic reviews, meta-analyses, clinical trials, and relevant case series that evaluated hemostatic abnormalities and

thrombotic complications in patients with α - or β -thalassemia. Conference abstracts, editorials, and studies with insufficient methodological detail were excluded. Titles and abstracts were screened for relevance, followed by full-text review of selected articles.

Data were extracted narratively, focusing on pathophysiological mechanisms, laboratory biomarkers, clinical risk factors, and thrombotic outcomes. Due to heterogeneity in study designs and outcome measures, a quantitative meta-analysis was not performed. Instead, findings were qualitatively synthesized to identify consistent patterns, emerging themes, and gaps in the current evidence base.

Pathophysiological Mechanisms of Coagulopathy in Thalassemia

Coagulopathy in thalassemia is a complex and multifactorial condition arising from an interplay between abnormal red blood cell (RBC) physiology, chronic hemolysis, endothelial dysfunction, platelet activation, and disturbances in coagulation and fibrinolytic pathways. These mechanisms collectively create a hypercoagulable state, particularly in patients with β -thalassemia intermedia and splenectomized individuals (Table 1)[12-13].

Table 1: Pathophysiological Mechanisms of Coagulopathy in Thalassemia

Mechanism	Key Molecular/Cellular Features	Effect on Hemostasis	Clinical Consequences
Abnormal red blood cell (RBC) membranes	Exposure of phosphatidylserine; oxidative membrane damage	Enhanced thrombin generation; promotion of coagulation complex assembly	Venous thromboembolism (VTE); microvascular thrombosis
Chronic platelet activation	Increased P-selectin expression; elevated β -thromboglobulin	Increased platelet aggregation and adhesion	Deep vein thrombosis (DVT); pulmonary embolism (PE)
Endothelial dysfunction	Nitric oxide (NO) scavenging by free hemoglobin; increased adhesion molecules	Prothrombotic endothelial surface; reduced vasodilation	Pulmonary hypertension; arterial thrombosis
Impaired natural anticoagulant	Reduced protein C, protein S, and antithrombin III levels	Loss of inhibition of thrombin and factor Xa	Recurrent thrombosis; hypercoagulable state

systems			
Procoagulant circulating microparticles	RBC- and platelet-derived microparticles rich in tissue factor	Amplification of coagulation cascade	Systemic activation of coagulation; DIC-like states
Inflammation and oxidative stress	Elevated cytokines (IL-6, TNF- α); increased ROS	Activation of coagulation and suppression of fibrinolysis	Chronic vascular injury; organ damage
Splenectomy-related changes	Increased circulating abnormal RBCs and platelets	Exaggerated hypercoagulable state	High risk of VTE, portal vein thrombosis
Impaired fibrinolysis	Elevated plasminogen activator inhibitor-1 (PAI-1)	Reduced clot breakdown	Persistent thrombosis; microcirculatory impairment

1. Abnormal Red Blood Cells and Phosphatidylserine Exposure

2.

Thalassemic RBCs often have altered membrane structure due to defective hemoglobin synthesis, leading to oxidative damage and premature destruction. These damaged erythrocytes expose phosphatidylserine (PS) on their outer membranes, which serves as a catalytic surface for the assembly of prothrombinase and tenase complexes. PS-exposing RBCs and microparticles derived from them significantly increase thrombin generation, contributing to the procoagulant state [14-15].

2. Chronic Hemolysis and Nitric Oxide Scavenging

Chronic intravascular hemolysis, a hallmark of thalassemia, releases free hemoglobin and heme into the plasma. Free hemoglobin binds and depletes nitric oxide (NO), a vasodilator and inhibitor of platelet aggregation. The resulting NO deficiency leads to vasoconstriction, increased platelet activation, and vascular inflammation, further promoting thrombogenesis [16-17].

3. Platelet Activation and Aggregation

Platelets in thalassemia patients exhibit heightened activation even in the absence of acute vascular injury. Studies have demonstrated increased expression of platelet activation markers such as P-selectin and CD63, as well as elevated thromboxane A2 levels. Splenectomized patients have higher circulating platelet counts

and a prolonged platelet lifespan, which augment the thrombotic burden. Furthermore, activated platelets release procoagulant microparticles that amplify thrombin generation [18].

4. Endothelial Dysfunction and Inflammation

Endothelial cells in thalassemia are chronically exposed to oxidative stress and inflammatory mediators, leading to endothelial activation and dysfunction. This results in the overexpression of adhesion molecules (e.g., ICAM-1, VCAM-1, E-selectin), facilitating leukocyte and platelet adhesion to the vascular wall. Additionally, increased levels of von Willebrand factor (vWF) and tissue factor expression on endothelial cells further accelerate coagulation cascade activation [19-21].

5. Iron Overload and Oxidative Stress

Iron overload, from both transfusion and increased gastrointestinal absorption, leads to the accumulation of labile plasma iron (LPI) and non-transferrin-bound iron (NTBI), which catalyze the formation of reactive oxygen species (ROS). These ROS induce endothelial injury, promote a proinflammatory state, and impair anticoagulant pathways. Iron-induced oxidative stress also compromises the function of antithrombotic proteins such as thrombomodulin and nitric oxide synthase [22-23].

6. Imbalance in Coagulation and Fibrinolysis

Thalassemia patients exhibit elevated levels of procoagulant factors, including factors VIII, IX, and XI, along with decreased levels of natural anticoagulants such as protein C, protein S, and antithrombin III. Concurrently, fibrinolysis is impaired due to increased levels of plasminogen activator inhibitor-1 (PAI-1). This imbalance favors clot formation and persistence, contributing to a sustained hypercoagulable state [24-25].

7. Role of Splenectomy

Splenectomy exacerbates coagulopathy by eliminating the spleen's filtering function, allowing damaged RBCs and activated platelets to persist in the circulation. Post-splenectomy patients often exhibit marked thrombocytosis and increased levels of PS-expressing cells and microparticles. This state is associated with a significantly higher incidence of venous thromboembolism (VTE) and stroke, particularly in NTDT populations [26-27].

Risk Factors for Thromboembolic Events in Thalassemia

Thalassemia patients are at increased risk of thromboembolic events (TEEs) due to a combination of disease-specific and treatment-related factors. Identifying these risk factors is critical for effective risk stratification and the implementation of preventive strategies. Several clinical and biological variables influence thrombotic risk, particularly in patients with β -thalassemia intermedia (TI) and non-transfusion-dependent thalassemia (NTDT) [28].

1. Splenectomy

Splenectomy is one of the most significant risk factors for TEEs in thalassemia. The spleen filters abnormal red cells and clears activated platelets and circulating microparticles. Following splenectomy, patients experience thrombocytosis and increased levels of procoagulant red cells and

microparticles. This leads to a sustained hypercoagulable state, particularly in older patients and those with TI, who often undergo splenectomy to reduce transfusion burden or manage hypersplenism [29-30].

2. Non-Transfusion-Dependent Thalassemia (NTDT)

Patients with NTDT, such as β -thalassemia intermedia, tend to have higher thrombotic risk than transfusion-dependent individuals. The lack of regular transfusions allows the accumulation of PS-expressing erythrocytes and ongoing hemolysis, which contribute to endothelial injury and thrombin generation. These patients also have more pronounced iron overload from increased intestinal absorption, further compounding vascular damage [31].

3. Age and Disease Duration

Thrombotic risk increases with age and cumulative disease burden. Older patients with longstanding hemolysis and iron overload are more likely to develop vascular complications. Chronic exposure to procoagulant stimuli and inflammation results in progressive endothelial dysfunction and atherosclerotic-like changes that elevate thrombotic potential [32].

4. Transfusion Practices

While transfusions can increase iron burden, regular blood transfusion reduces ineffective erythropoiesis and the number of abnormal circulating erythrocytes, thereby reducing the risk of thrombotic events. Irregular or inadequate transfusion regimens allow chronic hemolysis and PS-positive cells to persist, maintaining the prothrombotic state [33].

5. Iron Overload and Chelation Status

Severe iron overload is associated with vascular oxidative damage and endothelial dysfunction, both of which contribute to coagulopathy. Poor compliance or suboptimal dosing of iron chelation therapy increases the risk of iron-induced vascular

injury and thromboembolic complications. Chelators such as deferasirox and deferoxamine may have differing effects on inflammatory and oxidative pathways, which could influence thrombotic risk [34].

6. Elevated Platelet Counts and Activation

High platelet counts, especially following splenectomy, are associated with increased thrombotic risk. Even in the absence of thrombocytosis, platelets in thalassemia show spontaneous activation, contributing to platelet aggregation and thrombus formation. Platelet-derived microparticles further enhance coagulation by exposing PS and accelerating thrombin generation [35].

7. Genetic and Acquired Thrombophilia

Inherited thrombophilic disorders (e.g., factor V Leiden mutation, prothrombin gene mutation, protein C or S deficiency) may coexist in thalassemia patients and exacerbate the hypercoagulable state. Additionally, antiphospholipid antibodies and lupus anticoagulants have been reported in some thalassemia patients, suggesting an autoimmune component that may enhance thrombosis risk in a subset of individuals [36].

8. Inflammation and Endothelial Activation

Chronic inflammation, a hallmark of thalassemia, contributes to endothelial activation and expression of adhesion molecules. Increased levels of pro-inflammatory cytokines such as IL-6 and TNF- α further promote coagulation through enhanced tissue factor expression and fibrin deposition, especially in patients with poor iron control or frequent infections [37].

Clinical Consequences of Coagulopathy in Thalassemia

Coagulopathy in thalassemia is not merely a laboratory abnormality—it translates into significant clinical consequences that contribute

to long-term morbidity and, in some cases, mortality. The hypercoagulable state associated with both transfusion-dependent and non-transfusion-dependent thalassemia (NTDT) predisposes patients to a wide range of thrombotic complications, involving both the venous and arterial systems. These events often present insidiously and may be underdiagnosed, highlighting the need for increased clinical vigilance [38].

1. Venous Thromboembolism (VTE)

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are among the most well-documented thrombotic events in thalassemia, especially in splenectomized and NTDT patients. The incidence of VTE is significantly higher in these populations compared to the general public. DVTs typically affect the lower extremities but may occur in unusual sites such as the portal, mesenteric, and hepatic veins. PE may present with nonspecific symptoms such as dyspnea and chest pain, and it may be fatal if not promptly diagnosed and managed [39].

2. Arterial Thrombosis and Stroke

Although less common than venous events, arterial thromboses—including ischemic stroke and transient ischemic attacks (TIAs)—have been reported in both children and adults with thalassemia. Silent cerebral infarctions are particularly concerning in pediatric patients, as they may go undetected yet lead to neurocognitive impairment. The procoagulant environment, combined with endothelial dysfunction and platelet activation, increases the risk of cerebrovascular ischemic events, particularly in older or splenectomized patients [40].

3. Pulmonary Hypertension (PHT)

Pulmonary hypertension is a severe and potentially life-threatening complication of thalassemia, especially in NTDT patients. Chronic hemolysis contributes to NO depletion and vasoconstriction, while recurrent thromboembolism and in situ thrombosis in the

pulmonary vasculature exacerbate pulmonary vascular resistance. Over time, these changes can lead to right ventricular dysfunction, reduced exercise tolerance, and premature death [41].

4. Silent Infarcts and Cognitive Decline

Neuroimaging studies have revealed silent brain infarcts in a substantial proportion of thalassemia patients with no overt neurological symptoms. These infarcts are associated with subtle but progressive cognitive decline, including deficits in attention, memory, and executive function. Early identification and monitoring are essential to prevent long-term neuropsychological consequences, particularly in children and young adults [42].

5. Thrombosis in Unusual Sites

Thrombosis may also occur in less common anatomical locations such as retinal vessels, the portal vein system, or even cardiac chambers. These atypical events are more frequent in splenectomized patients and those with markedly elevated platelet counts or iron overload. Retinal vein occlusion, for example, may lead to vision impairment, while portal vein thrombosis can cause abdominal pain and liver dysfunction [43].

6. Cardiac Complications

Although primarily attributed to iron overload, coagulopathy may also contribute to cardiac complications in thalassemia. Thrombosis in the coronary microcirculation and endothelial dysfunction can synergize with iron-induced cardiomyopathy to impair myocardial perfusion. These effects may accelerate the progression of heart failure in transfusion-dependent individuals [44].

Diagnostic Evaluation

The diagnostic evaluation of coagulopathy in thalassemia requires a comprehensive approach that combines clinical assessment, laboratory investigations, and imaging studies. Given the

often subclinical nature of the hypercoagulable state in these patients, especially in non-transfusion-dependent thalassemia (NTDT), early and proactive screening is crucial to identify individuals at risk of thromboembolic events (TEEs) before the onset of overt complications [45]. A thorough clinical history should include an assessment of prior thrombotic events, splenectomy status, transfusion history, and the presence of comorbidities such as liver dysfunction or cardiac disease. Physical examination findings may be nonspecific but should include careful evaluation for signs of deep vein thrombosis, pulmonary hypertension, or neurologic deficits. Patients with known risk factors—such as older age, splenectomy, and NTDT phenotype—warrant closer surveillance [46].

Basic coagulation studies are essential initial tests and include prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels, and D-dimer. While these may be normal in many patients, elevated D-dimer and prothrombin fragments (F1+2) may suggest ongoing activation of the coagulation cascade. Thrombin-antithrombin (TAT) complexes and elevated levels of factor VIII can also indicate hypercoagulability. Thalassemia patients may also exhibit decreased levels of natural anticoagulants such as protein C, protein S, and antithrombin III, which should be measured especially in those with unexplained or recurrent thrombosis [47]. In addition to routine tests, platelet function assays may be useful to evaluate spontaneous platelet activation, particularly in splenectomized individuals. Flow cytometry can detect phosphatidylserine (PS)-expressing red cells and microparticles, both of which are considered markers of procoagulant activity in thalassemia. Inflammation markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) may also provide insight into underlying endothelial activation and systemic inflammatory status, which further contribute to coagulopathy [48].

Imaging studies are indispensable when thromboembolic events are suspected. Doppler ultrasound is the preferred modality for detecting

deep vein thrombosis in the limbs, while CT pulmonary angiography is used to diagnose pulmonary embolism. For patients with neurologic symptoms or those at risk of silent cerebral infarcts, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain are recommended. Echocardiography, particularly with Doppler evaluation, can help assess pulmonary artery pressure and identify early signs of pulmonary hypertension [49]. Iron overload should also be evaluated routinely as it is a key driver of oxidative stress and endothelial dysfunction. Serum ferritin levels, though widely used, can be influenced by inflammation and may not accurately reflect tissue iron stores. More precise quantification of iron burden is achieved through MRI-based assessment of liver iron concentration (LIC) and cardiac T2* values [51].

Management of Coagulopathy in Thalassemia

The management of coagulopathy in thalassemia requires a multifaceted approach aimed at addressing underlying pathophysiological mechanisms, reducing thrombotic risk, and managing existing complications. Tailoring treatment based on individual risk factors such as splenectomy status, transfusion dependence, iron overload, and prior thrombotic events is essential to optimize outcomes. The strategies below integrate preventive, therapeutic, and supportive interventions.

1. Risk-Based Thromboprophylaxis

Preventive anticoagulation may be considered in high-risk patients, particularly those who are splenectomized, have a history of thrombosis, or present with significantly elevated platelet counts and laboratory evidence of hypercoagulability. Low-dose aspirin is commonly used for thromboprophylaxis in non-transfusion-dependent thalassemia (NTDT), especially post-splenectomy. In select high-risk patients, particularly those with a history of venous thromboembolism (VTE), long-term

anticoagulation with agents such as low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs) may be warranted under careful monitoring [52].

2. Optimization of Transfusion Therapy

Regular transfusion therapy plays a protective role against coagulopathy by suppressing ineffective erythropoiesis, reducing circulating phosphatidylserine-expressing red blood cells, and limiting hemolysis. In NTDT patients with evidence of hypercoagulability or prior thrombotic events, initiating a transfusion program may reduce thrombotic risk. However, this must be balanced against the risk of iron overload, necessitating close monitoring and concurrent chelation therapy [53].

3. Iron Chelation Therapy

Iron overload promotes oxidative stress and endothelial dysfunction, both of which contribute to coagulopathy. Effective chelation therapy—using agents such as deferoxamine, deferasirox, or deferiprone—is essential to reduce labile plasma iron and mitigate vascular injury. Chelation not only prevents organ damage but also improves vascular homeostasis and may indirectly reduce thrombotic risk [54].

4. Post-Splenectomy Monitoring and Management

Patients who have undergone splenectomy require long-term surveillance for thrombotic complications. Platelet counts should be regularly monitored, and antiplatelet therapy may be initiated if counts are persistently elevated. In cases of extreme thrombocytosis or additional risk factors, more aggressive anticoagulation strategies may be considered. These patients also benefit from periodic imaging (e.g., Doppler ultrasound, echocardiography) to detect subclinical thrombosis or pulmonary hypertension [55].

5. Management of Established Thrombotic Events

In patients who develop VTE or arterial thrombosis, standard treatment protocols apply, including initial anticoagulation with LMWH followed by long-term therapy with warfarin or DOACs. The duration of therapy should be individualized, considering recurrence risk and bleeding potential. In cases of stroke or cerebrovascular events, management includes not only anticoagulation but also neurorehabilitation and risk factor modification [56].

6. Role of Emerging Therapies

Novel agents such as luspatcept, which improve ineffective erythropoiesis and hemoglobin levels, may reduce the chronic hemolysis and erythroid stress that contribute to coagulopathy. Although their direct effect on thrombosis risk is still under investigation, these agents hold promise in modifying the underlying disease milieu and potentially lowering prothrombotic tendencies [57-59].

7. Lifestyle and Supportive Measures

Patients should be counseled on general thromboembolism prevention measures, including adequate hydration, early ambulation during hospital stays, and avoiding prolonged immobilization. Smoking cessation, weight control, and management of comorbid conditions such as diabetes and hypertension are important in minimizing vascular risk. Patient education and regular follow-up are essential components of long-term management [60-61].

Conclusion

Coagulopathy in thalassemia represents a complex interplay of multiple pathophysiological mechanisms including chronic hemolysis, platelet activation, endothelial dysfunction, and iron overload, which collectively contribute to a heightened thrombotic risk. This hypercoagulable state is particularly pronounced in splenectomized and non-transfusion-dependent patients,

underscoring the heterogeneity of thrombotic risk across thalassemia subtypes. The clinical consequences are diverse and impactful, ranging from venous thromboembolism and arterial strokes to pulmonary hypertension and silent cerebral infarcts, all of which significantly impair quality of life and increase morbidity and mortality. Early recognition through vigilant clinical assessment and targeted laboratory and imaging evaluations is essential for timely diagnosis and risk stratification. Despite advances in understanding the underlying mechanisms, the management of coagulopathy in thalassemia remains challenging due to the balance required between preventing thrombosis and minimizing bleeding risks, especially in a population already burdened by chronic anemia and iron overload complications.

References

1. Sadiq IZ, Abubakar FS, Usman HS, Abdullahi AD, Ibrahim B, Kastayal BS, Ibrahim M, Hassan HA. Thalassemia: Pathophysiology, Diagnosis, and Advances in Treatment. *Thalassemia Reports*. 2024; 14(4):81-102. <https://doi.org/10.3390/thalassrep14040010>
2. Dordevic A, Mrakovic-Sutic I, Pavlovic S, Ugrin M, Roganovic J. Beta thalassemia syndromes: New insights. *World J Clin Cases*. 2025;13(10):100223. doi: 10.12998/wjcc.v13.i10.100223.
3. Farmakis D, Porter J, Taher A, Domenica Cappellini M, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. *Hemisphere*. 2022;6(8): e732. doi: 10.1097/HS9.0000000000000732.
4. Nienhuis AW, Nathan DG. Pathophysiology and Clinical Manifestations of the β -Thalassemias. *Cold Spring Harb Perspect Med*. 2012;2(12): a011726. doi: 10.1101/cshperspect.a011726.
5. Al-Sanabra OM, Abbas MA, Hazà WJ, Hazà AA, Al Tibi AK. Coagulation and Fibrinolysis Dysregulation in β -Thalassemia Major:

- Potential Impact of Splenectomy and Medications on Thrombotic Risk. *Clin Appl ThrombHemost.* 2025; 31:10760296251359291. doi: 10.1177/10760296251359291.
6. Cappellini MD, Musallam KM, Marcon A, Taher AT. Coagulopathy in Beta-thalassemia: current understanding and future perspectives. *Mediterr J Hematol Infect Dis.* 2009;1(1): e2009029. doi: 10.4084/MJHID.2009.029.
 7. Obeagu EI. Thalassemia in Sub-Saharan Africa: epidemiology, diagnosis, and management - a narrative review. *Ann Med Surg (Lond).* 2025;87(6):3523-3536. doi: 10.1097/MS9.0000000000003270.
 8. Taher AT, Saliba AN. Iron overload in thalassemia: different organs at different rates. *Hematology Am Soc Hematol Educ Program.* 2017;2017(1):265-271. doi: 10.1182/asheducation-2017.1.265.
 9. Pinto VM, Forni GL. Management of Iron Overload in Beta-Thalassemia Patients: Clinical Practice Update Based on Case Series. *Int J Mol Sci.* 2020;21(22):8771. doi: 10.3390/ijms21228771.
 10. Ahmadi A, Hosseini S, Dorgalaleh A, Hassani S, Tabibian S, Tavasoli B, Shabannezhad A, Taheri M, Shams M. Natural Anticoagulant Protein Levels in Patients with Beta-Thalassemia Major: A Case-Control Study. *J Hematol.* 2024;13(1-2):23-28. doi: 10.14740/jh1217.
 11. Abd El Mabood S, Fahmy DM, Akef A, El Sallab S. Protein C and Anti-Thrombin-III Deficiency in Children with Beta-Thalassemia. *J Hematol.* 2018;7(2):62-68. doi: 10.14740/jh392w.
 12. Cappellini MD, Musallam KM, Marcon A, Taher AT. Coagulopathy in Beta-thalassemia: current understanding and future perspectives. *Mediterr J Hematol Infect Dis.* 2009;1(1): e2009029. doi: 10.4084/MJHID.2009.029.
 13. Al-Sanabra OM, Abbas MA, Hazà WJ, Hazà AA, Al Tibi AK. Coagulation and Fibrinolysis Dysregulation in β -Thalassemia Major: Potential Impact of Splenectomy and Medications on Thrombotic Risk. *Clin Appl ThrombHemost.* 2025; 31:10760296251359291. doi: 10.1177/10760296251359291.
 14. Chansai S, Yamsri S, Fucharoen S, Fucharoen G, Teawtrakul N. Phosphatidylserine-exposed red blood cells and ineffective erythropoiesis biomarkers in patients with thalassemia. *Am J Transl Res.* 2022;14(7):4743-4756.
 15. Obeagu EI. Thalassemia in Sub-Saharan Africa: epidemiology, diagnosis, and management—a narrative review. *Annals of Medicine and Surgery.* 2025 Jun 1;87(6):3523-36.
 16. Zahedpanah M, Azarkeivan A, Aghaiepour M, Nikogoftar M, Ahmadinegad M, Hajibeigi B, Tabatabaiee MR, Maghsudlu M. Erythrocytic phosphatidylserine exposure and hemostatic alterations in β -thalassemia intermediate patients. *Hematology.* 2014;19(8):472-476. doi: 10.1179/1607845413Y.0000000148.
 17. Kato GJ, Taylor JG 6th. Pleiotropic effects of intravascular haemolysis on vascular homeostasis. *Br J Haematol.* 2010;148(5):690-701. doi: 10.1111/j.1365-2141.2009.08004.x.
 18. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. *J Clin Invest.* 2017;127(3):750-760. doi: 10.1172/JCI89741.
 19. Succar J, Musallam KM, Taher AT. Thalassemia and venous thromboembolism. *Mediterr J Hematol Infect Dis.* 2011;3(1): e2011025. doi: 10.4084/MJHID.2011.025.
 20. Chuljerm H, Maneekeorn S, Thorup G, Nantakool S, Charoenkwan P, Rerkasem K. The Relevance of Endothelial Dysfunction Biomarkers in Thalassemia Patients and Healthy Individuals: A Systematic Review and Meta-Analysis. *Int J Mol Sci.* 2025;26(8):3842. doi: 10.3390/ijms26083842.
 21. Dri E, Lampas E, Lazaros G, Lazarou E, Theofilis P, Tsioufis C, Tousoulis D. Inflammatory Mediators of Endothelial Dysfunction. *Life.* 2023; 13(6):1420. <https://doi.org/10.3390/life13061420>
 22. Theofilis P, Sigris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C, Tousoulis D. Inflammatory Mechanisms

- Contributing to Endothelial Dysfunction. *Biomedicines*. 2021;9(7):781. doi: 10.3390/biomedicines9070781.
23. Duca L, Di Pierro E, Scaramellini N, Granata F, Graziadei G. The Relationship Between Non-Transferrin-Bound Iron (NTBI), Labile Plasma Iron (LPI), and Iron Toxicity. *Int J Mol Sci*. 2025;26(13):6433. doi: 10.3390/ijms26136433.
24. Fernandes MS, Rissi TT, Zuravski L, Mezzomo J, Vargas CR, Folmer V, Soares FA, Manfredini V, Ahmed M, Puntel RL. Oxidative stress and labile plasmatic iron in anemic patients following blood therapy. *World J Exp Med*. 2014;4(3):38-45. doi: 10.5493/wjem. v4. i3.38.
25. Al-Sanabra OM, Abbas MA, Hazà WJ, Hazà AA, Al Tibi AK. Coagulation and Fibrinolysis Dysregulation in β -Thalassemia Major: Potential Impact of Splenectomy and Medications on Thrombotic Risk. *Clin Appl ThrombHemost*. 2025; 31:10760296251359291. doi: 10.1177/10760296251359291.
26. Ahmadi A, Hosseini S, Dorgalaleh A, Hassani S, Tabibian S, Tavasoli B, Shabannezhad A, Taheri M, Shams M. Natural Anticoagulant Protein Levels in Patients With Beta-Thalassemia Major: A Case-Control Study. *J Hematol*. 2024;13(1-2):23-28. doi: 10.14740/jh1217.
27. Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. *Blood*. 2009;114(14):2861-8. doi: 10.1182/blood-2009-04-210112.
28. J H, Acharya S, Huse S, Sachdev A. Reactive Thrombocytosis: A Bizarre Consequence of Splenectomy. *Cureus*. 2024;16(4): e57455. doi: 10.7759/cureus.57455.
29. Succar J, Musallam KM, Taher AT. Thalassemia and venous thromboembolism. *Mediterr J Hematol Infect Dis*. 2011;3(1): e2011025. doi: 10.4084/MJHID.2011.025.
30. Birsin Z, Salihoğlu A, Tokdil KO, Pirdal BZ, Bilgiç S, Avcı BK, Özmen D, Eşkazan AE, Ar MC, Başlar Z, Elverdi T. Is splenectomy one of the contributory factors to pulmonary hypertension? An analysis of splenectomized hemolytic anemia and immune thrombocytopenia patients. *Ann Hematol*. 2025;104(9):4447-4456. doi: 10.1007/s00277-025-06583-9.
31. Obeagu EI, Obeagu GU. Screening for thalassemia traits in pregnancy: the role of Mentzer index. *International Journal of Medical Sciences and Pharma Research*. 2024;10(4):50-55.
32. Kalamara TV, Dodos K, Vlachaki E. Splenectomy is significantly associated with thrombosis but not with pulmonary hypertension in patients with transfusion-dependent thalassemia: a meta-analysis of observational studies. *Front Med (Lausanne)*. 2023; 10:1259785. doi: 10.3389/fmed.2023.1259785.
33. Shash H. Non-Transfusion-Dependent Thalassemia: A Panoramic Review. *Medicina (Kaunas)*. 2022;58(10):1496. doi: 10.3390/medicina58101496.
34. Młodziński K, Świętaczak M, Rohun J, Wolf J, Narkiewicz K, Hellmann M, Daniłowicz-Szymanowicz L. Vascular Aging and Damage in Patients with Iron Metabolism Disorders. *Diagnostics (Basel)*. 2022;12(11):2817. doi: 10.3390/diagnostics12112817.
35. Karafin MS, Kelly S, Chapman KM, Kreuziger LB, Manis JP, Dinardo C, Josephson CD, Stone M, Roubinian NH, Branchford B, Sachais BS, Hailu B, Sabino EC, Hod EA, Custer B; National Heart, Lung, and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study-IV-Pediatric (REDS-IV-P). The Red Blood Cell-Improving Transfusions for Chronically Transfused Recipients (RBC-IMPACT) study: protocol description of an international multi-site observational clinical study. *Blood Transfus*. 2025;23(5):418-432. doi: 10.2450/BloodTransfus.1026.
36. Entezari S, Haghi SM, Norouzkhani N, Sahebazar B, Vosoughian F, Akbarzadeh D, Islampanah M, Naghsh N, Abbasalizadeh M, Deravi N. Iron Chelators in Treatment of Iron Overload. *J Toxicol*. 2022; 2022:4911205. doi: 10.1155/2022/4911205.
37. Khan PN, Nair RJ, Olivares J, Tingle LE, Li Z. Postsplenectomy reactive thrombocytosis.

- Proc (Bayl Univ Med Cent). 2009;22(1):9-12. doi: 10.1080/08998280.2009.11928458.
38. Robeva R, Tanev D, Andonova S, Nikolova M, Tomova A, Kumanov P, Savov A, Rashkov R, Kolarov Z. Inherited Thrombophilias Could Influence the Reproductive Outcome in Women with Systemic Lupus Erythematosus. *Balkan J Med Genet.* 2017;20(1):21-26. doi: 10.1515/bjmg-2017-0011.
39. Caprari P, Profumo E, Massimi S, Buttari B, Riganò R, Regine V, Gabbianelli M, Rossi S, Risoluti R, Materazzi S, Gullifa G, Maffei L, Sorrentino F. Hemorheological profiles and chronic inflammation markers in transfusion-dependent and non-transfusion-dependent thalassemia. *Front Mol Biosci.* 2023; 9:1108896. doi: 10.3389/fmolb.2022.1108896.
40. Cappellini MD, Musallam KM, Marcon A, Taher AT. Coagulopathy in Beta-thalassemia: current understanding and future perspectives. *Mediterr J Hematol Infect Dis.* 2009;1(1): e2009029. doi: 10.4084/MJHID.2009.029.
41. Obeagu EI. Coagulation abnormalities in pediatric anemia clinical and laboratory correlates for risk stratification and risk assessment. *Annals of Medicine and Surgery.* 2026;88(1):644-652.
42. Basnet A, Acharya B, Shrestha M, Thapa S. Deep Vein Thrombosis in a Patient with Thalassemia Minor: A Case Report. *Clin Case Rep.* 2025;13(11): e71497. doi: 10.1002/ccr3.71497.
43. Ciccone S, Cappella M, Borgna-Pignatti C. Ischemic stroke in infants and children: practical management in emergency. *Stroke Res Treat.* 2011; 2011:736965. doi: 10.4061/2011/736965.
44. Fraidenburg DR, Machado RF. Pulmonary hypertension associated with thalassemia syndromes. *Ann N Y Acad Sci.* 2016;1368(1):127-39. doi: 10.1111/nyas.13037.
45. DeBaun MR, Armstrong FD, McKinsty RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. *Blood.* 2012;119(20):4587-4596. doi: 10.1182/blood-2011-02-272682.
46. Dong F, Luo SH, Zheng LJ, Chu JG, Huang H, Zhang XQ, Yao KC. Incidence of portal vein thrombosis after splenectomy and its influence on transjugular intrahepatic portosystemic shunt stent patency. *World J Clin Cases.* 2019;7(17):2450-2462. doi: 10.12998/wjcc. v7. i17.2450.
47. Lekawanvijit S, Chattipakorn N. Iron overload thalassemic cardiomyopathy: iron status assessment and mechanisms of mechanical and electrical disturbance due to iron toxicity. *Can J Cardiol.* 2009;25(4):213-218. doi: 10.1016/s0828-282x (09)70064-9.
48. Cappellini MD, Musallam KM, Marcon A, Taher AT. Coagulopathy in Beta-thalassemia: current understanding and future perspectives. *Mediterr J Hematol Infect Dis.* 2009;1(1): e2009029. doi: 10.4084/MJHID.2009.029.
49. Kalamara TV, Dodos K, Vlachaki E. Splenectomy is significantly associated with thrombosis but not with pulmonary hypertension in patients with transfusion-dependent thalassemia: a meta-analysis of observational studies. *Front Med (Lausanne).* 2023; 10:1259785. doi: 10.3389/fmed.2023.1259785.
50. Yamada S, Asakura H. How We Interpret Thrombosis with Thrombocytopenia Syndrome? *International Journal of Molecular Sciences.* 2024; 25(9):4956. <https://doi.org/10.3390/ijms25094956>
51. Jourdi G, Ramström S, Sharma R, Bakchoul T, Lordkipanidzé M; FC-PFT in TP study group. Consensus report on flow cytometry for platelet function testing in thrombocytopenic patients: communication from the SSC of the ISTH. *J ThrombHaemost.* 2023;21(10):2941-2952. doi: 10.1016/j.jtha.2023.07.006.
52. Moore AJE, Wachsmann J, Chamrathy MR, Panjikaran L, Tanabe Y, Rajiah P. Imaging of acute pulmonary embolism: an update. *Cardiovasc Diagn Ther.* 2018;8(3):225-243. doi: 10.21037/cdt.2017.12.01.
53. Triggiani S, Pellegrino G, Mortellaro S, Bubba A, Lanza C, Carriero S, Biondetti P, Angileri SA, Fusco R, Granata V, Carrafiello

- G. Comprehensive review of pulmonary embolism imaging: past, present and future innovations in computed tomography (CT) and other diagnostic techniques. *Jpn J Radiol.* 2025;43(10):1575-1589. doi: 10.1007/s11604-025-01811-8.
54. Wang Z, Fang S, Ding S, Tan Q, Zhang X. Research Progress on Relationship Between Iron Overload and Lower Limb Arterial Disease in Type 2 Diabetes Mellitus. *Diabetes MetabSyndrObes.* 2022; 15:2259-2264. doi: 10.2147/DMSO.S366729.
55. Al-Sanabra OM, Abbas MA, Hazà WJ, Hazà AA, Al Tibi AK. Coagulation and Fibrinolysis Dysregulation in β -Thalassemia Major: Potential Impact of Splenectomy and Medications on Thrombotic Risk. *Clin Appl ThrombHemost.* 2025; 31:10760296251359291. doi: 10.1177/10760296251359291.
56. Chansai S, Yamsri S, Fucharoen S, Fucharoen G, Teawtrakul N. Phosphatidylserine-exposed red blood cells and ineffective erythropoiesis biomarkers in patients with thalassemia. *Am J Transl Res.* 2022;14(7):4743-4756.
57. Kontoghiorghe CN, Kontoghiorghes GJ. Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes. *Drug Des DevelTher.* 2016; 10:465-81. doi: 10.2147/DDDT.S79458.
58. Khan PN, Nair RJ, Olivares J, Tingle LE, Li Z. Postsplenectomy reactive thrombocytosis. *Proc (Bayl Univ Med Cent).* 2009;22(1):9-12. doi: 10.1080/08998280.2009.11928458.
59. Hong J, Ahn SY, Lee YJ, Lee JH, Han JW, Kim KH, Yhim HY, Nam SH, Kim HJ, Song J, Kim SH, Bang SM, Kim JS, Mun YC, Bae SH, Kim HK, Jang S, Park R, Choi HS, Kim I, Oh D; Korean Society of Hematology Thrombosis and Hemostasis Working Party. Updated recommendations for the treatment of venous thromboembolism. *Blood Res.* 2021;56(1):6-16. doi: 10.5045/br.2021.2020083.
60. Musallam KM, Taher AT. Luspatercept: a treatment for ineffective erythropoiesis in thalassemia. *Hematology Am Soc Hematol Educ Program.* 2024;2024(1):419-425. doi: 10.1182/hematology.2024000567.
61. Lau BD, Murphy P, Nastasi AJ, Seal S, Kraus PS, Hobson DB, Shaffer DL, Holzmueller CG, Aboagye JK, Streiff MB, Haut ER. Effectiveness of ambulation to prevent venous thromboembolism in patients admitted to hospital: a systematic review. *CMAJ Open.* 2020;8(4): E832-E843. doi: 10.9778/cmajo.20200003.

Abbreviations

DVT – Deep vein thrombosis
 NO – Nitric oxide
 PE – Pulmonary embolism
 RBC – Red blood cell
 ROS – Reactive oxygen species
 TIA – Transient ischemic attack
 VTE – Venous thromboembolism
 WHO – World Health Organization

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