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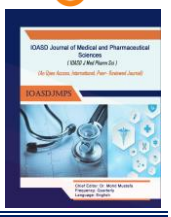

Hemostatic Imbalance in Thalassemia: From Molecular Mechanisms to Clinical Manifestations

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ABSTRACT

Thalassemia is a hereditary hemoglobinopathy characterized by defective globin chain synthesis, leading to chronic anemia and systemic complications. Among these, hemostatic imbalance has gained increasing attention due to its contribution to significant morbidity and mortality. This review explores the complex molecular mechanisms underpinning coagulation disturbances in thalassemia, including chronic hemolysis-induced endothelial dysfunction, platelet activation, microparticle generation, and coagulation factor alterations. These pathophysiological changes foster a prothrombotic state while occasionally predisposing to bleeding complications. Clinically, patients with thalassemia exhibit a broad spectrum of hemostatic manifestations ranging from thromboembolic events such as deep vein thrombosis and stroke to bleeding tendencies associated with platelet dysfunction and coagulopathy. Diagnostic evaluation is complicated by overlapping clinical features and the limitations of routine coagulation assays, necessitating more advanced testing modalities to accurately assess coagulation status and guide management. The impact of factors such as splenectomy, iron overload, and oxidative stress on hemostasis further complicates clinical care. Effective management of hemostatic imbalance in thalassemia requires a multidisciplinary approach that balances thrombotic and bleeding risks. Current strategies include anticoagulation, iron chelation, and careful monitoring of coagulation parameters. Advances in molecular diagnostics and emerging targeted therapies offer promising avenues for personalized care. This review underscores the importance of understanding hemostatic alterations in thalassemia to improve clinical outcomes and highlights areas for future research.

Keywords: Thalassemia, Hemostatic imbalance, Coagulation disorders, Hypercoagulability, Molecular mechanisms.

Review Article

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INTRODUCTION

Thalassemia is a group of inherited hemoglobin disorders caused by mutations that reduce or abolish the synthesis of one or more globin chains, resulting in defective hemoglobin formation and chronic anemia [1-2]. The disease manifests in varying degrees of severity, from the mild, often asymptomatic thalassemia trait, to the severe transfusion-dependent thalassemia major. Globally, thalassemia represents a significant public health concern, particularly in regions such as the Mediterranean basin, the Middle East, South and Southeast Asia, and parts of Africa, where the prevalence remains high. Advances in transfusion medicine and iron chelation therapy have markedly improved life expectancy, shifting the clinical focus toward managing long-term complications that include endocrinopathies, organ damage, and increasingly recognized coagulation abnormalities [3-5]. Hemostatic imbalance in thalassemia patients is a complex and multifactorial phenomenon that contributes significantly to morbidity and mortality. Historically, thalassemia was considered primarily a disease of anemia and ineffective erythropoiesis, but recent evidence has underscored the prothrombotic tendency in affected individuals. Paradoxically, while thrombotic events are a major concern, bleeding complications have also been reported, creating a clinical dilemma. This hemostatic dysregulation results from an interplay of pathophysiological factors including chronic hemolysis,

endothelial dysfunction, platelet activation, and coagulation factor disturbances [6-7].

The pathogenesis of hemostatic imbalance begins with chronic hemolysis, a hallmark of thalassemia, which releases free hemoglobin and other erythrocyte contents into the circulation. This process leads to nitric oxide (NO) scavenging, reduced NO bioavailability, and subsequent endothelial dysfunction. Endothelial cells play a pivotal role in maintaining vascular homeostasis; their activation and injury induce a procoagulant state by upregulating adhesion molecules, promoting leukocyte and platelet adherence, and triggering coagulation cascades. Furthermore, oxidative stress and iron overload—consequences of repeated blood transfusions and ineffective erythropoiesis—exacerbate endothelial damage, amplifying coagulation abnormalities [8-9]. Platelet abnormalities in thalassemia further contribute to hemostatic imbalance. Studies demonstrate increased platelet activation, aggregation, and an elevated number of circulating platelet-derived microparticles, which provide a catalytic surface for thrombin generation. These microparticles are highly procoagulant and are considered important mediators in thrombogenesis. Additionally, quantitative and qualitative platelet defects contribute to bleeding risks, complicating therapeutic decisions in patients who often require anticoagulation for thrombotic complications [10-11].

Coagulation factor imbalances are another critical aspect of hemostatic disturbance in thalassemia. Elevated levels of procoagulant factors such as factor VIII and von Willebrand factor have been observed alongside reduced activity of natural anticoagulants including protein C, protein S, and antithrombin. This imbalance skews the hemostatic system towards hypercoagulability. Moreover, fibrinolytic activity is often impaired, reducing the breakdown of fibrin clots and favoring persistent thrombosis. These changes, coupled with altered liver function due to iron overload, contribute to the complexity of coagulopathy in thalassemia [12-13]. Clinically, the consequences of hemostatic imbalance are diverse. Thromboembolic events such as deep vein thrombosis, pulmonary embolism, and ischemic stroke are increasingly recognized complications, especially in splenectomized patients and those with thalassemia intermedia. On the other hand, bleeding manifestations, often related to thrombocytopenia, platelet dysfunction, or liver disease, may present significant clinical challenges. These dual risks require careful clinical evaluation and tailored therapeutic strategies to mitigate both bleeding and thrombotic complications [14-15].

AIM

The primary aim of this review is to provide a comprehensive synthesis of current knowledge on hemostatic imbalance in thalassemia, emphasizing the underlying molecular mechanisms and their translation into clinical manifestations.

METHODS

This narrative review was conducted through a comprehensive, non-systematic search of the published literature to explore mechanisms and clinical implications of hemostatic imbalance in thalassemia. Electronic databases including PubMed, Scopus, and Google Scholar were searched for English-language articles using combinations of keywords such as *thalassemia*, *hemostatic imbalance*, *hypercoagulability*, *thrombosis*, *platelet activation*, *endothelial dysfunction*, and *coagulation abnormalities*. Original research articles, narrative and systematic reviews, observational studies, and relevant consensus statements were considered. Priority was given to studies addressing molecular and cellular mechanisms, laboratory evidence of coagulation dysregulation, and clinically documented thrombotic or bleeding manifestations in thalassemia. Reference lists of selected articles were manually screened to identify additional relevant publications. Data were synthesized descriptively without formal meta-analysis, integrating experimental, translational, and clinical evidence to provide a coherent overview of current understanding. Emphasis was placed on linking mechanistic insights with clinical phenotypes and therapeutic implications, consistent with the narrative review methodology.

Molecular Mechanisms Underpinning Hemostatic Imbalance

Hemostatic imbalance in thalassemia arises from a complex interplay of molecular and cellular disturbances that disrupt the finely tuned equilibrium between procoagulant and anticoagulant forces. Central to this dysregulation is chronic hemolysis, a defining feature of thalassemia, which leads to the release of free hemoglobin, heme, and other erythrocyte-derived products into the circulation. Free hemoglobin avidly scavenges nitric oxide (NO), a critical vasodilator and inhibitor of platelet aggregation and leukocyte adhesion. The consequent depletion of NO results in endothelial dysfunction, characterized by increased expression of adhesion molecules, enhanced platelet binding, and a proinflammatory state that fosters thrombogenesis [16-17]. Endothelial activation in thalassemia is further aggravated by oxidative stress and iron overload, common sequelae of frequent blood transfusions and ineffective erythropoiesis. Excessive iron catalyzes the formation of reactive oxygen species (ROS), which damage endothelial cells, impair anticoagulant pathways, and promote a shift toward a prothrombotic phenotype. Activated endothelial cells release increased amounts of von Willebrand factor (vWF), tissue factor, and other procoagulant mediators, enhancing platelet adhesion and coagulation cascade activation. Additionally, the endothelium's diminished production of anticoagulant molecules such as prostacyclin and

thrombomodulin further tips the balance in favor of clot formation [18-19].

Platelets also play a pivotal role in the hemostatic imbalance observed in thalassemia. Multiple studies have demonstrated heightened platelet activation and aggregation, as well as an increased number of circulating platelet-derived microparticles. These microparticles provide a catalytic surface for thrombin generation and amplify the coagulation response. The molecular triggers for this platelet hyperactivity include exposure to proinflammatory cytokines, oxidative stress, and interaction with damaged endothelium. However, despite the prothrombotic platelet phenotype, qualitative platelet defects and quantitative thrombocytopenia can coexist, increasing bleeding risk in some patients and complicating clinical management [20-21]. At the level of coagulation proteins, patients with thalassemia commonly exhibit elevated levels of procoagulant factors such as factor VIII and vWF, which contribute to hypercoagulability. Conversely, natural anticoagulant proteins—including protein C, protein S, and antithrombin—are often reduced or functionally impaired. This imbalance is exacerbated by liver dysfunction secondary to iron overload, which affects the synthesis and clearance of coagulation factors. Furthermore, fibrinolytic system abnormalities, including reduced plasminogen activity and elevated levels of plasminogen activator inhibitor-1 (PAI-1), lead to impaired clot breakdown, thus sustaining thrombi and increasing the risk of vascular occlusion [22-23]. The interplay of these molecular mechanisms results in a unique and dynamic hemostatic environment in thalassemia, characterized by simultaneous prothrombotic and hemorrhagic tendencies. The heterogeneity of these molecular alterations underscores the need for individualized diagnostic and therapeutic approaches, as the balance between bleeding and clotting risks varies widely among patients depending on factors such as genotype, transfusion status, iron load, and splenectomy history. A deeper understanding of these molecular pathways is essential for the development of targeted interventions aimed at restoring hemostatic equilibrium and improving clinical outcomes (Table 1) [24-25].

Table 1: Molecular Mechanisms Underpinning Hemostatic Imbalance in Thalassemia

Mechanism	Description	Impact on Hemostasis / Clinical Implication
Red Blood Cell Membrane Abnormalities	Phosphatidylserine externalization, oxidative damage, and membrane rigidity in thalassemic RBCs	Provides catalytic surface for thrombin generation; promotes microvascular occlusion and hypercoagulability
Chronic Hemolysis	Release of free hemoglobin and arginase	Scavenges nitric oxide (NO), impairs vasodilation, contributes to endothelial dysfunction and pulmonary hypertension
Platelet Activation	Increased P-selectin expression, elevated platelet-derived microparticles	Enhances thrombin generation, increases thrombotic risk, especially post-splenectomy
Endothelial Dysfunction	Upregulation of adhesion molecules, tissue factor, and inflammatory cytokines	Promotes leukocyte adhesion, local coagulation activation, and vascular prothrombotic state
Coagulation Cascade Activation	Elevated thrombin-antithrombin complexes, prothrombin fragment 1+2	Direct activation of clotting pathways leading to hypercoagulability
Natural Anticoagulant Deficiency	Reduced levels of protein C, protein S, and antithrombin III	Impairs endogenous anticoagulation, shifting balance toward thrombosis
Circulating Microparticles (MPs)	Derived from RBCs, platelets, and endothelium, expressing phospholipids and tissue factor	Amplify thrombin generation and propagate coagulation systemically
Chronic Inflammation	Elevated cytokines (e.g., IL-6, TNF-α) and acute-phase reactants	Enhances coagulation cascade and endothelial activation, perpetuating thrombotic risk
Oxidative Stress	Excess reactive oxygen species (ROS) from ineffective erythropoiesis	Damages vascular endothelium and RBC membranes, promoting hypercoagulability

Clinical Manifestations of Hemostatic Imbalance

The hemostatic imbalance observed in thalassemia manifests clinically through a spectrum of thrombotic and hemorrhagic complications that significantly impact patient morbidity and mortality. Thromboembolic events have gained prominence as a major clinical concern, particularly in patients with thalassemia intermedia and those who have undergone splenectomy. Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), represents one of the most frequent thrombotic complications. Additionally, arterial thromboses such as ischemic stroke and peripheral arterial occlusion have been reported, underscoring the systemic nature of the prothrombotic state in this population [26-27]. Several factors predispose thalassemia patients to thrombotic events. Splenectomy, commonly performed to reduce hemolysis and transfusion requirements, leads to an increased circulating load of damaged erythrocytes, activated platelets, and procoagulant microparticles, all of which amplify thrombin generation. Iron overload and chronic inflammation further exacerbate endothelial dysfunction and coagulation activation. Clinically, thrombosis may

present with limb swelling, pain, neurological deficits, or respiratory distress depending on the affected vascular territory, often necessitating urgent intervention [28-29].

Conversely, bleeding manifestations, though less frequent, remain a significant clinical challenge. Bleeding tendencies in thalassemia arise primarily from thrombocytopenia, platelet dysfunction, and coexisting liver disease that impairs synthesis of clotting factors. Mucocutaneous bleeding, epistaxis, gum bleeding, and menorrhagia are common presentations. More severe bleeding, such as gastrointestinal hemorrhage or intracranial bleeding, is less common but can be life-threatening. Importantly, the coexistence of bleeding and thrombotic risks complicates clinical decision-making, particularly concerning anticoagulant use [30-31]. In pediatric populations, these hemostatic complications may influence growth, development, and quality of life. Early identification of at-risk children is essential, as thrombotic events in young patients can lead to long-term disability. Furthermore, the subtlety of bleeding symptoms often delays diagnosis until significant clinical consequences arise. Routine surveillance and thorough clinical evaluation tailored to the patient's individual risk profile are therefore critical components of comprehensive thalassemia care [32-33]. Hemostatic imbalance also contributes to microvascular complications, such as pulmonary hypertension and leg ulcers, which reflect ongoing endothelial injury and thrombosis in the microcirculation. Pulmonary hypertension, in particular, is a severe complication associated with increased mortality and is thought to result from repeated microthrombotic events combined with chronic hemolysis-induced vascular remodeling. Similarly, chronic leg ulcers may reflect localized ischemia secondary to impaired microcirculatory flow and coagulation abnormalities [34-35].

Laboratory Evaluation of Hemostatic Imbalance in Thalassemia

The laboratory evaluation of hemostatic imbalance in thalassemia is a critical component in understanding the extent and nature of coagulation disturbances, guiding clinical management and therapeutic decisions. Given the complex interplay of prothrombotic and bleeding risks, a comprehensive and multimodal laboratory approach is essential to accurately characterize the hemostatic profile of affected patients [36]. Routine coagulation tests provide the initial framework for evaluation. These typically include prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), and fibrinogen levels. In thalassemia patients, PT and aPTT are often within normal limits but may be prolonged in cases complicated by liver dysfunction or factor deficiencies. Fibrinogen levels are generally normal or elevated, reflecting a chronic inflammatory state. However, these conventional assays have limited sensitivity to detect subtle or early hypercoagulability and do not fully capture the dynamic interactions within the coagulation cascade in thalassemia [37].

Advanced global coagulation assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have increasingly been employed to provide a real-time, comprehensive assessment of clot formation, strength, and lysis. These assays offer valuable insights into the balance of coagulation and fibrinolysis, identifying hypercoagulable states that conventional tests may miss. Studies in thalassemia populations have demonstrated altered viscoelastic profiles consistent with enhanced clot firmness and reduced fibrinolysis, supporting the clinical observation of a prothrombotic tendency [38]. Measurement of specific coagulation factors further elucidates the underlying abnormalities. Elevated levels of factor VIII and von Willebrand factor (vWF) antigen are common findings, reflecting endothelial activation and contributing to increased thrombin generation. Conversely, deficiencies or functional impairments in natural anticoagulants such as protein C, protein S, and antithrombin have been documented, particularly in patients with iron overload and hepatic involvement. Assessment of these parameters is essential in comprehensive risk stratification [39].

Platelet function testing is another vital aspect of laboratory evaluation, given the dual role of platelets in promoting thrombosis and bleeding in thalassemia. Tests such as platelet aggregometry, flow cytometry for platelet activation markers (e.g., P-selectin), and measurement of circulating platelet-derived microparticles provide insights into platelet hyperreactivity or dysfunction. The results are often heterogeneous, mirroring the clinical variability observed in this population [40]. Markers of fibrinolytic activity, including plasminogen levels, tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1), are also important to assess. Elevated PAI-1 and reduced fibrinolytic activity have been implicated in sustaining thrombi and contributing to chronic vascular complications such as pulmonary hypertension [41]. Emerging molecular and genetic assays offer promising tools for evaluating predisposition to coagulation disorders in thalassemia. Identification of polymorphisms in genes encoding coagulation factors, platelet receptors, or fibrinolytic proteins may enhance personalized risk prediction and guide therapeutic interventions in the future [42].

Management Strategies

The management of hemostatic imbalance in thalassemia is multifaceted, aiming to reduce both thrombotic and bleeding risks while addressing the underlying pathophysiological contributors. Due to the dual risk of thrombosis and hemorrhage, individualized treatment plans based on comprehensive clinical and laboratory evaluations are paramount to optimizing outcomes [43].

Prevention and Treatment of Thrombosis

Thromboembolic complications represent a significant clinical challenge, especially in thalassemia intermedia patients and those post-splenectomies. Prophylactic strategies primarily focus on minimizing known risk factors, including careful consideration of splenectomy indications, stringent iron chelation to reduce iron overload, and control of chronic inflammation. Anticoagulation therapy is commonly employed in patients with documented thrombosis or those deemed at high risk, using agents such as low molecular weight heparin (LMWH), warfarin, or newer oral anticoagulants. However, the decision to initiate anticoagulation must carefully weigh bleeding risks, and close monitoring is essential [44].

Management of Bleeding

Bleeding tendencies, although less common than thrombosis, require prompt recognition and intervention. Management includes correction of thrombocytopenia and platelet dysfunction, often through transfusions of platelets or fresh frozen plasma in severe cases. Addressing underlying liver dysfunction is also critical, as hepatic impairment can exacerbate clotting factor deficiencies. Supportive measures such as local hemostatic agents and iron supplementation to reduce ineffective erythropoiesis may be beneficial. Hormonal therapy can be considered for managing menorrhagia in female patients [45-46].

Role of Blood Transfusions and Iron Chelation

Regular blood transfusions remain a cornerstone in thalassemia management by suppressing ineffective erythropoiesis and reducing hemolysis, indirectly ameliorating hemostatic abnormalities. However, transfusions contribute to iron overload, which worsens endothelial dysfunction and coagulopathy. Therefore, rigorous iron chelation therapy using agents like deferasirox or deferoxamine is critical to mitigate these adverse effects. Optimal chelation not only improves hepatic function but may also reduce thrombotic risk by attenuating oxidative stress and vascular injury [47].

Emerging Therapeutic Approaches

Recent advances have explored the potential of novel therapies targeting specific molecular pathways involved in coagulation imbalance. These include agents modulating platelet activation, endothelial function, and fibrinolysis. For example, statins have demonstrated endothelial-protective and anti-inflammatory effects that may benefit thalassemia patients. Additionally, research into gene therapy and genome editing offers future promise for correcting the underlying globin gene defects, potentially normalizing hemostatic function [48].

Multidisciplinary and Supportive Care

Effective management necessitates a multidisciplinary approach involving hematologists, cardiologists, hepatologists, and transfusion specialists to address the complex complications of thalassemia. Regular screening for thrombotic and bleeding events, as well as monitoring of coagulation parameters, is vital. Patient education on symptom recognition and adherence to therapy is equally important in preventing complications [49].

Tailoring Treatment to Individual Risk Profiles

Given the heterogeneity in clinical presentation and hemostatic profiles, treatment strategies should be tailored to individual risk factors such as genotype, transfusion status, splenectomy history, and comorbidities. Risk stratification models incorporating clinical and laboratory data can guide therapeutic decisions and improve prognosis [50].

Advances in Molecular Diagnostics and Genetic Profiling

Molecular diagnostics and genetic profiling have revolutionized the evaluation of hemostatic imbalances in thalassemia by enabling the identification of underlying genetic variants that modulate coagulation pathways. Technologies such as next-generation sequencing (NGS) allow comprehensive analysis of genes implicated in coagulation and platelet function, including those encoding coagulation factors (e.g., Factor V, Factor II), natural anticoagulants (e.g., protein C, protein S), and fibrinolytic proteins. This comprehensive genetic insight is vital, as thalassemia patients often harbor coexisting genetic thrombophilic mutations, which synergistically increase thrombotic risk [51]. Furthermore, molecular profiling assists in differentiating inherited coagulation disorders from acquired abnormalities related to thalassemia pathophysiology, such as iron overload and endothelial dysfunction. Transcriptomic and proteomic studies have identified altered expression of endothelial adhesion molecules, platelet activation markers, and inflammatory cytokines, which contribute to the hypercoagulable state. These advances facilitate personalized risk assessment and targeted therapies [52]. The incorporation of genetic testing into clinical practice is also instrumental in family counseling and early detection of at-risk individuals. However, challenges remain in interpreting variants of uncertain significance and integrating these data into practical management algorithms. Ongoing research to expand genotype-phenotype correlations is critical to fully harness the potential of molecular diagnostics in this field [53].

Innovations in Global Coagulation Assays

Traditional coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) offer limited insight into the dynamic and complex process of coagulation, especially in thalassemia where hemostatic imbalance is multifactorial. Global coagulation assays like thromboelastography (TEG) and rotational thromboelastometry (ROTEM) provide comprehensive,

real-time analysis of clot formation, stabilization, and lysis by measuring viscoelastic properties of whole blood [54]. In thalassemia patients, TEG and ROTEM have uncovered hypercoagulable profiles characterized by shortened clotting times and increased clot strength, even when standard tests remain normal. These assays detect subtle coagulation abnormalities, including platelet contribution and fibrinolytic activity, allowing more accurate assessment of thrombotic risk. They also guide transfusion strategies and anticoagulation management by monitoring coagulation dynamics during treatment [55]. The clinical utility of global assays extends to perioperative settings and monitoring of iron chelation therapy effects on coagulation. Despite their advantages, limitations include the need for standardized protocols, specialized training, and cost considerations. Future developments aim to improve assay sensitivity and incorporate them into routine coagulation monitoring in thalassemia care [56].

Role of Platelet Function Testing and Biomarkers

Platelets play a central role in the hemostatic disturbances seen in thalassemia, often exhibiting hyperactivation despite thrombocytopenia in some cases. Advanced platelet function testing methodologies, including flow cytometry to detect activation markers (such as P-selectin and PAC-1 binding), aggregometry to assess responsiveness to agonists, and measurement of circulating platelet-derived microparticles, have enhanced the understanding of platelet behavior in these patients [57]. Elevated levels of platelet microparticles, which are procoagulant and inflammatory, have been associated with increased vascular complications and thrombosis. These biomarkers provide objective measures of platelet activation state and can serve as prognostic indicators. Furthermore, platelet function tests help distinguish between qualitative platelet defects and quantitative deficiencies, aiding therapeutic decision-making regarding the use of antiplatelet agents [58]. Emerging biomarkers such as thromboxane B2, soluble CD40 ligand, and markers of oxidative stress are under investigation for their roles in modulating platelet function and vascular injury in thalassemia. The integration of platelet biomarkers with clinical data may improve individualized risk stratification and optimize antithrombotic therapies [59].

Impact of Developmental Hemostasis on Diagnostic Interpretation

Developmental hemostasis refers to the physiological changes in coagulation factor levels, platelet function, and fibrinolytic activity that occur from birth through early childhood. In pediatric patients with thalassemia, especially those aged 0-5 years, these normal maturational changes complicate the interpretation of coagulation tests, risking misdiagnosis or missed diagnosis of hemostatic disorders [60]. Neonates and young children typically exhibit reduced levels of vitamin K-dependent factors (II, VII, IX, X), naturally prolonged PT and aPTT, and immature platelet function. These age-related variations necessitate the use of age-specific reference ranges when evaluating coagulation parameters. Failure to account for developmental hemostasis can result in inappropriate management decisions, such as unnecessary anticoagulation or failure to detect bleeding risk [61].

Integration of Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) applications are transforming the landscape of hemostatic disorder diagnostics and management in thalassemia by enabling analysis of complex and multidimensional datasets. ML algorithms can integrate clinical parameters, laboratory test results, genetic profiles, and imaging data to identify patterns predictive of thrombosis or bleeding complications [62-63]. Predictive models developed through AI can assist clinicians in stratifying patients by risk, optimizing timing and dosing of anticoagulant or transfusion therapies, and detecting early signs of hemostatic imbalance. For example, AI-based tools can analyze trends in global coagulation assays, platelet function tests, and biomarker levels to recommend personalized treatment adjustments [64]. Moreover, AI enhances research by identifying novel biomarkers and molecular signatures associated with coagulopathy in large datasets, accelerating discovery. Despite promising results, challenges include data standardization, interpretability of AI outputs, and ensuring integration into clinical workflows. Continued collaboration between clinicians, data scientists, and engineers is vital to realize AI's full potential in improving care for thalassemia patients [65].

Multidisciplinary Care Models and Telemedicine

The complexity of hemostatic imbalance in thalassemia demands a multidisciplinary approach involving hematologists, cardiologists, hepatologists, transfusion specialists, and laboratory scientists. Collaborative care models enable comprehensive management of thrombotic and bleeding risks, iron overload complications, and organ dysfunction [66]. Regular multidisciplinary team meetings facilitate individualized treatment planning, incorporating clinical status, laboratory findings, and imaging results. This approach has been shown to improve patient outcomes by ensuring timely interventions and coordinated follow-up [67]. Telemedicine has emerged as a valuable adjunct, particularly for patients in remote or resource-limited settings. Remote consultations, electronic health records, and mobile health applications enable continuous monitoring of coagulation parameters and symptoms, facilitating early detection of complications. Telemedicine improves access to specialist care, patient education, and adherence to therapy, thereby reducing hospitalizations and healthcare costs [68]. The expansion of telemedicine platforms, combined with multidisciplinary care, promises to enhance the quality and equity of care for thalassemia patients worldwide.

Emerging Therapeutics and Personalized Management

Recent therapeutic advances focus on correcting specific molecular defects and modulating the hemostatic system to balance bleeding and thrombotic risks in thalassemia. Novel anticoagulants with improved safety profiles, such as direct oral anticoagulants (DOACs), are being evaluated for use in this population, potentially reducing the need for frequent monitoring associated with traditional agents [61]. Targeted therapies addressing platelet hyperactivation and endothelial dysfunction are under investigation, including antiplatelet agents and statins with anti-inflammatory and endothelial-stabilizing properties. Moreover, agents that modulate fibrinolysis may offer additional benefits in preventing thrombotic complications [60].

Cutting-edge approaches like gene therapy and genome editing (e.g., CRISPR-Cas9) aim to correct the underlying globin gene mutations responsible for thalassemia, thereby potentially normalizing coagulation abnormalities. These strategies, while still largely experimental, represent transformative potential for future management [11]. Personalized medicine, integrating genetic, molecular, and clinical data, enables tailored treatment plans optimizing efficacy and minimizing adverse effects. As therapeutic options expand, ongoing clinical trials and real-world studies will inform best practices for individualized management of hemostatic imbalance in thalassemia [12].

CONCLUSION

Hemostatic imbalance in thalassemia represents a complex and multifactorial challenge that significantly impacts patient morbidity and mortality. The intricate interplay between prothrombotic tendencies and bleeding risks underscores the necessity for comprehensive clinical and laboratory evaluation to guide effective management. Molecular mechanisms such as endothelial dysfunction, platelet activation, and coagulation factor abnormalities form the biological foundation of this imbalance, translating into a broad spectrum of clinical manifestations ranging from venous and arterial thrombosis to hemorrhagic complications. Advancements in diagnostic technologies, including global coagulation assays, platelet function tests, and genetic profiling, have enhanced the understanding and detection of hemostatic disturbances in thalassemia, facilitating more accurate risk stratification. Concurrently, evolving management strategies—spanning optimized transfusion regimens, iron chelation, anticoagulation, and emerging targeted therapies—offer promising avenues for mitigating complications. The integration of multidisciplinary care models and personalized treatment plans tailored to individual risk profiles remains paramount.

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