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Digital Technologies and Artificial Intelligence in the Diagnosis, Monitoring, and Prevention of Thalassemia: Current Status, Limitations, and Future Perspectives

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ABSTRACT

Thalassemia is a prevalent hereditary blood disorder that requires early diagnosis, continuous monitoring, and long-term management. In recent years, digital technologies and artificial intelligence have emerged as potential tools to enhance various aspects of thalassemia care. This narrative review aims to critically evaluate current evidence on the use of artificial intelligence in the diagnosis, monitoring, treatment support, and prevention of thalassemia.

Available studies indicate that machine learning models applied to routine hematologic parameters can improve the differentiation between thalassemia and iron deficiency anemia, and may support large-scale carrier screening, particularly in resource-limited settings. Artificial intelligence has also been explored in medical image analysis, including automated assessment of iron overload using magnetic resonance imaging, as well as in the digital evaluation of blood cell morphology. In addition, emerging applications include prediction of clinical outcomes, support for transfusion and chelation therapy decisions, and integration with telemedicine for remote patient monitoring.

Despite these advances, most artificial intelligence applications in thalassemia remain at an early or investigational stage. Major limitations include small and non-representative datasets, limited external validation, challenges related to model interpretability, and barriers to integration into clinical workflows. Ethical and regulatory considerations further complicate implementation, particularly in areas involving genetic data and high-stakes clinical decision-making.

Overall, artificial intelligence has significant potential to improve diagnostic accessibility, optimize screening strategies, and support individualized patient management in thalassemia. However, its routine clinical adoption will depend on rigorous validation, standardization, and demonstration of real-world clinical utility.

Keywords: thalassemia; artificial intelligence; digital technologies; machine learning; deep learning; diagnosis; monitoring; prevention; telemedicine; hematology

Introduction

Thalassemia is a group of inherited disorders caused by impaired synthesis of globin chains and is among the most common monogenic diseases worldwide[1-2]. Its clinical spectrum ranges from asymptomatic carrier states and mild anemia to severe transfusion-dependent conditions requiring lifelong transfusion support and iron chelation therapy[3-9]. A substantial subgroup also includes patients with non-transfusion-dependent thalassemia, in whom transfusion requirements are lower but the risk of chronic complications remains clinically significant[4,7-8].

Management includes early diagnosis, regular monitoring of complications, assessment of iron overload, evaluation of target-organ involvement, and timely therapeutic adjustment [3-11]. Prevention programs aimed at carrier detection, genetic counseling, and prenatal diagnosis are likewise central to thalassemia care[12]. Clinical management is further complicated by marked phenotypic variability related to genetic heterogeneity and modifying factors[13].

Standard diagnostic evaluation relies on clinical assessment, complete blood count, red blood cell indices, hemoglobin fraction analysis, and molecular confirmation.[9-11] Although these methods are clinically indispensable, their use may be limited by access to specialized laboratories, cost, turnaround time, and interpretative difficulties in selected settings. This is particularly relevant in differentiating thalassemia from iron deficiency anemia, as both conditions may present with similar hematologic features but require different management strategies[14] .

In recent years, digital technologies and artificial intelligence (AI) have emerged as potential tools to enhance diagnostic accuracy, optimize transfusion decision-making, and support longitudinal management of patients with thalassemia within modern transfusion medicine systems [15-21] . In hematology, AI has already been explored in laboratory classification, image analysis, clinical outcome prediction, and decision support.[15-16,18,22-23] However, the clinical maturity of these applications remains uneven, and their practical value in thalassemia requires careful appraisal.

Thalassemia represents not only a hematological disorder but also a global public health challenge, particularly in regions with limited access to specialized diagnostics and long-term monitoring. The emergence of digital health technologies and artificial intelligence offers an opportunity to bridge gaps between resource-rich and resource-limited healthcare systems.

The aim of this review is to summarize current evidence on the use of digital technologies and artificial intelligence in the diagnosis, monitoring, treatment, and prevention of thalassemia, and to identify the principal limitations and future directions in this field.

This review discusses current applications of AI in diagnosis, monitoring, therapy optimization, and prevention, followed by an analysis of ethical considerations and future clinical perspectives.

Rather than providing a purely descriptive overview, this review aims to critically integrate current evidence and identify clinically meaningful trends emerging from recent research.

Methods of Review

This study is a narrative review of the literature on the application of digital technologies and artificial intelligence in thalassemia. The analysis included clinical guidelines, review articles, original studies, and selected preliminary publications published predominantly between 2017 and 2026. The literature was grouped into the following domains: general aspects of thalassemia and its management; applications of AI in medicine and hematology; AI in thalassemia diagnosis; digital monitoring and telemedicine; AI in prevention, genetic screening, and counseling; and methodological, ethical, and regulatory aspects of medical AI.

Interpretation of the literature was informed by general principles for the evaluation of predictive models and AI systems in medicine, including transparency and reporting standards [24-25]. This review is not a systematic review or meta-analysis and does not include quantitative synthesis. Accordingly, its conclusions should be interpreted as an analytical overview of the available literature rather than a formal assessment of the level of evidence.

Sources were selected from publications indexed in international bibliographic databases and relevant medical resources, including clinical guidelines, review articles, original studies, and selected preliminary reports. Priority was given to publications directly addressing the diagnosis, monitoring, prevention, and treatment of thalassemia, as well as studies focused on the use of artificial intelligence in medicine and hematology. Additional attention was given to methodological publications addressing development, validation, interpretability, and reporting of AI models. Given the narrative design of this review, no formal search protocol, standardized study selection process, or meta-analytic synthesis was performed.

Current Status

The principal domains of AI application in thalassemia are summarized in Figure 2 , while key opportunities and limitations across these domains are outlined in Table 2.

Artificial Intelligence in Thalassemia Diagnosis

Accurate and timely diagnosis of thalassemia is essential both for treatment planning and for the implementation of prevention programs (Table 1A). In routine clinical practice, diagnosis is based on clinical assessment, complete blood count, red blood cell indices, hemoglobin fraction analysis, and molecular confirmation.[9-11] One of the main diagnostic challenges lies in differentiating thalassemia from iron deficiency anemia, since both conditions may present with microcytosis and hypochromia but require different clinical management[14].

Table 1A. Key studies on artificial intelligence in the diagnosis and differential diagnosis of thalassemia

First author	Year	Study type	Focus	Key contribution
Laengsri V et al.	2019	Original study	Web-based machine learning tool	ThalPred model for distinguishing thalassemia trait vs iron deficiency anemia
Erten M et al.	2022	Original study	Machine learning classification	Automated differentiation using feature selection methods
Tepakhan W et al.	2025	Original study	Random Forest / Gradient Boosting	High-performance machine learning models for IDA vs thalassemia
Hataysal EP et al.	2025	Original study	RBC-based machine learning	Prediction using erythrocyte indices
Mo D et al.	2023	Original study	Deep learning	Neural network prediction of thalassemia probability
Lv J et al.	2025	Original study	Machine learning classification	Discrimination of microcytic hypochromic anemia
Gui Y et al.	2026	Original study	AI morphology	Automated RBC morphology analysis
Mazzuca D et al.	2024	Applied study	Image-based AI	Blood smear-based diagnostic approach

At present, one of the most developed areas of AI application in thalassemia is the analysis of routine hematologic data (Figure 1). In several studies, models based on red blood cell parameters demonstrated the ability to distinguish thalassemia, iron deficiency anemia, and other microcytic hypochromic conditions[26-32]. A practical example is ThalPred, a web-based tool developed to discriminate thalassemia trait from iron deficiency anemia[26]. Other studies have explored the use of Random Forest, Gradient Boosting, and related machine learning approaches for interpreting standard laboratory parameters[27-29,31].

Figure 1. AI integration into the diagnostic workflow for thalassemia.

Integration of artificial intelligence into the diagnostic workflow for thalassemia, including data collection, preprocessing, model-based analysis, and clinical decision support using hematologic, imaging, and clinical data.

Beyond reported classification performance, the clinical translation of machine learning models based on complete blood count parameters warrants careful consideration. Although multiple studies demonstrate high accuracy in differentiating thalassemia from iron deficiency anemia, such results are often derived from controlled datasets and may not fully reflect real-world conditions. Variability in pre-analytical and analytical factors—including differences in hematology analyzers, laboratory calibration, and population-specific reference ranges—may substantially influence model performance. In addition, the presence of coexisting conditions, such as inflammation, pregnancy, or combined nutritional deficiencies, may further complicate interpretation. Consequently, the generalizability and robustness of these models remain key challenges. Future investigations should therefore prioritize external validation across heterogeneous populations, as well as direct comparison with established discrimination indices, to determine whether machine learning approaches provide clinically meaningful incremental value.

Additional interest has focused on hybrid models combining fuzzy logic and machine learning, which have been investigated for identifying β-thalassemia carriers using standard hematologic features [32] (Table 1B). Deep neural networks have also been studied for predicting the probability of thalassemia based on routine red blood cell indices [30]. Furthermore, machine learning algorithms have been explored for the detection of α- and β-thalassemia carriers, which may be relevant to screening strategies [33-34].

Table 1B. Key studies on artificial intelligence in thalassemia screening, carrier detection, and genetic modeling

First author	Year	Study type	Focus	Key contribution
Ibrahim M et al.	2024	Original study	Fuzzy + machine learning model	Prediction of β-thalassemia carriers
Mohammadi E et al.	2025	Original study	Machine learning screening	Detection of alpha-thalassemia carriers
Das R et al.	2022	Original study	Screening algorithms	Antenatal screening using machine learning vs formulas
Younas HA et al.	2026	Original / review	Federated learning	Privacy-preserving carrier prediction
Abbas M et al.	2025	Original study	Explainable AI	Interpretable models for carrier prediction
Zhan L et al.	2023	Review	Sequencing technologies	Integration with genetic diagnostics
Traeger-Synodinos J et al.	2017	Review	Carrier screening	Clinical framework for prevention strategies

An important distinction should be made between conventional discrimination indices and data-driven machine learning models. Traditional indices derived from complete blood count parameters are typically based on predefined mathematical relationships and may perform inconsistently across different populations and laboratory settings. By contrast, machine learning models can capture more complex multivariable patterns and nonlinear interactions among routine hematologic parameters. This may partly explain their better performance in some studies, particularly when multiple red blood cell indices are analyzed simultaneously rather than interpreted in isolation.

Even so, diagnostic performance metrics alone should not be treated as evidence of clinical utility. High internal accuracy or area under the curve does not necessarily translate into reliable real-world performance. For AI-based diagnostic tools to be clinically meaningful, they should ideally demonstrate calibration, external validation across diverse populations, and stable performance under varying pre-analytical and analytical conditions. In thalassemia, these issues are particularly important because hematologic profiles may differ according to genotype, coexisting iron deficiency, age group, pregnancy status, and population background. Future studies should therefore move beyond proof-of-concept performance and focus on reproducibility, transportability, and prospective evaluation in routine care settings.

Overall, current findings should be interpreted with caution. Most models have been evaluated on limited datasets, and evidence regarding external validation and cross-population transportability remains restricted [21,23]. AI tools should therefore currently be regarded as methods for preliminary assessment and clinical support rather than replacements for laboratory and molecular diagnostic testing.

Importantly, the potential clinical utility of these models extends beyond diagnostic accuracy alone, encompassing their role as triage tools that may streamline diagnostic pathways, reduce unnecessary confirmatory testing, and improve overall workflow efficiency.

Genotype-Phenotype Modeling

The clinical heterogeneity of thalassemia is largely determined by the underlying genetic variant, the presence of modifying factors, and population-specific features. Studies on genotype-phenotype correlations have shown that individual mutations are associated with differences in disease severity,

hemoglobin levels, transfusion requirements, and the spectrum of complications[13]. These observations provide a basis for more precise prediction of clinical course.

Artificial intelligence is being considered as a potential tool for analyzing complex nonlinear relationships among clinical, laboratory, genetic, and imaging data [21,23]. Machine learning algorithms may be used for preliminary estimation of the probability of certain genetic variants and for stratifying the risk of severe disease [35-36]. Such approaches are of particular interest in settings where access to extended molecular testing is limited.

At present, however, AI-based genotype-phenotype modeling remains largely investigational. These approaches are constrained by limited sample sizes, heterogeneity of input data, and insufficient external validation. Accordingly, such models cannot be considered a substitute for molecular confirmation of the diagnosis.

Medical Image Analysis

One of the most clinically important complications of transfusion-dependent thalassemia is iron overload involving the heart and liver. Magnetic resonance imaging with T2* assessment plays a major role in monitoring myocardial and hepatic iron burden. In this area, AI—particularly deep learning—may be used for automated segmentation of anatomical structures and for standardizing measurements.

Studies on automated MRI analysis have shown that deep learning may improve the reproducibility of myocardial T2* assessment and reduce operator dependence.[37] Another emerging direction is digital analysis of red blood cell morphology and peripheral blood smear images, which has been investigated as a potential tool for screening hemoglobinopathies and other anemias[38-39].

The evidence in this field remains relatively limited, and some publications are exploratory or application-oriented. Broader implementation of such tools will require standardized imaging protocols, independent external validation, and assessment of clinical utility in real-world practice.[21,23]

Patient Monitoring and Telemedicine

Thalassemia requires long-term follow-up, regular laboratory monitoring, assessment of treatment response, and timely detection of complications. In this context, digital technologies and telemedicine may improve continuity of care and access to specialized services, particularly for patients living in remote areas.[40-42]

Experience gained during the COVID-19 pandemic demonstrated that telemedicine models can be adapted for the care of patients with chronic and hematologic diseases [41-42]. In thalassemia, such platforms may potentially be used for remote symptom monitoring, laboratory result review, treatment adherence tracking, and surveillance of adverse effects.

The integration of telemedicine solutions with AI-based analytical tools also creates opportunities for predictive monitoring and earlier identification of adverse changes[15,18,23]. Nonetheless, data on the clinical effectiveness of such approaches specifically in thalassemia remain limited, and their practical value requires further study.

Translating these technological advances into routine clinical practice remains the central challenge rather than algorithm development itself.

POTENTIAL ROLE OF ARTIFICIAL INTELLIGENCE IN THERAPY PERSONALIZATION

Transfusion Therapy

Transfusion support remains one of the core components of care for patients with transfusion-dependent thalassemia [3,5]. In clinical practice, decisions regarding the frequency and volume of transfusions are based on hemoglobin level, clinical status, rate of hemoglobin decline, signs of

tissue hypoxia, body weight, and the presence of complications. AI may potentially be used to integrate these factors into predictive models of transfusion requirements[16,23,35-36].

Another possible application is the assessment of transfusion-related risks, including alloimmunization, and support for safer transfusion strategies. However, current evidence in this area remains limited, and most proposed solutions are still at the stage of early development, conceptual discussion, or preliminary clinical evaluation.

Chelation Therapy

Chelation therapy is essential for the prevention and treatment of iron overload in patients receiving regular transfusions [3,5]. Selection of the chelating agent, treatment regimen, and dose depends on serum ferritin levels, cardiac and hepatic MRI T2*, treatment tolerance, age, comorbidities, and adherence. In this context, AI may be viewed as a tool for integrating heterogeneous clinical data to support a more individualized therapeutic approach[16,23,35-37].

In the future, such models may help predict treatment response, the likelihood of adverse effects, and the need to modify therapy. Before broader clinical use, however, studies are needed to demonstrate reliability, reproducibility, and added value compared with standard clinical practice.

Support for Complex Clinical Decision-Making

A critical distinction in the application of artificial intelligence in thalassemia lies between predictive modeling and true clinical decision support. While numerous models are capable of estimating risk or predicting clinical outcomes, their transformation into clinically actionable decision-support systems requires integration with existing workflows, prospective validation, and demonstration of added value beyond expert clinical judgment. In complex, chronic conditions such as thalassemia, where management decisions are influenced by multiple interdependent variables, effective decision-support tools must also account for temporal dynamics and longitudinal patient trajectories rather than relying solely on static inputs.

One of the most challenging issues in the management of selected patients with severe thalassemia is determining the timing and appropriateness of hematopoietic stem cell transplantation. This decision depends on genotype, clinical severity, transfusion burden, degree of iron overload, organ function, donor availability, and the expected risk of transplant-related complications [3-4,7].

In theory, AI could be used to integrate these variables into risk stratification and outcome prediction models [16,18,23,35-36]. Such systems might support clinicians in estimating the probability of transplant success, the risk of complications, and long-term survival. At present, however, these approaches remain insufficiently validated and cannot be considered a standalone basis for clinical decision-making. The potential consequences of error are particularly serious in this setting, which necessitates cautious interpretation of any algorithm-based recommendations.

An additional consideration relates to the potential risks associated with algorithm-assisted decision-making. In high-stakes clinical contexts—such as determination of transplant eligibility or modification of transfusion strategies—erroneous predictions may have significant clinical consequences. Accordingly, artificial intelligence systems should be designed to augment, rather than replace, clinician expertise, with explicit acknowledgment of uncertainty and clear delineation of model limitations.

Future development of clinical decision-support systems should emphasize explainability, real-time integration with electronic health records, and prospective evaluation of their impact on clinically meaningful outcomes.

Artificial Intelligence in Thalassemia Prevention

Prevention is of particular importance in regions with a high prevalence of thalassemia carrier states. Its key components include population screening, carrier detection, genetic counseling, and prenatal diagnosis.[12] In these areas, AI may be useful primarily as a tool for preliminary triage and risk stratification.

From a population health perspective, the application of artificial intelligence in screening and carrier detection should be evaluated within the context of structured diagnostic pathways rather than as isolated classification tools. In high-prevalence settings, machine learning–based models may serve as an initial triage layer, enabling prioritization of individuals for confirmatory molecular testing and thereby improving the cost-effectiveness of screening programs. However, such strategies inherently involve trade-offs between sensitivity and specificity. False-negative results may delay diagnosis and appropriate counseling, whereas false-positive classifications may increase healthcare utilization and contribute to patient anxiety. Accordingly, optimal model deployment requires careful calibration to local epidemiological characteristics and healthcare system capacity.

Machine learning algorithms can use routine hematologic data to identify individuals with a high probability of thalassemia carrier status[26,32-34]. This may be especially relevant in resource-limited settings, where molecular testing cannot be used as the first-line approach for the entire population. Explainable AI models may further improve transparency of predictions and trust in their use for genetic counseling[43]. In this context, interpretability assumes particular importance, as algorithmic outputs may directly influence genetic counseling, reproductive decision-making, and communication of risk. Transparent and explainable models may therefore enhance both clinician confidence and patient understanding, facilitating their integration into ethically sensitive clinical scenarios.

The implementation of AI-assisted screening may be particularly transformative in low- and middle-income countries, where shortages of trained specialists limit early diagnosis. Mobile-based and cloud-supported diagnostic systems may enable decentralized screening strategies.

Interpretability is particularly important in thalassemia because algorithmic outputs may influence clinically and ethically sensitive decisions, including referral for confirmatory testing, reproductive counseling, and risk communication. In this context, explainable AI may provide not only technical transparency but also clinical reassurance by identifying which variables contribute most strongly to a prediction. This is especially relevant when models are built from routine hematologic data, where clinicians may reasonably expect to understand why a patient is classified as having a high probability of carrier status.

It is also useful to distinguish between inherently interpretable models and post hoc explanation methods. The former aim to preserve transparency at the model level, whereas the latter attempt to explain predictions generated by more complex algorithms after model training. Both approaches may have a role in thalassemia-related applications, but their clinical acceptability will likely depend on the decision context. For example, a model used for large-scale preliminary screening may tolerate a somewhat lower level of interpretability than one used to support individualized counseling or other high-stakes decisions. Accordingly, future research should assess not only predictive performance, but also how explanations are understood and used by clinicians, laboratory specialists, and patients.

Additional perspectives are linked to ongoing advances in molecular diagnostics, including next-generation and third-generation sequencing, which expand the possibilities for accurate diagnosis and population screening[11-12,44]. At the

public health level, AI may also be used to analyze demographic and epidemiologic data, optimize screening programs, and support more rational allocation of resources[21,45]. The broader role of AI across screening, prevention, and public health applications is also illustrated in Figure 2 and summarized in Table 2.

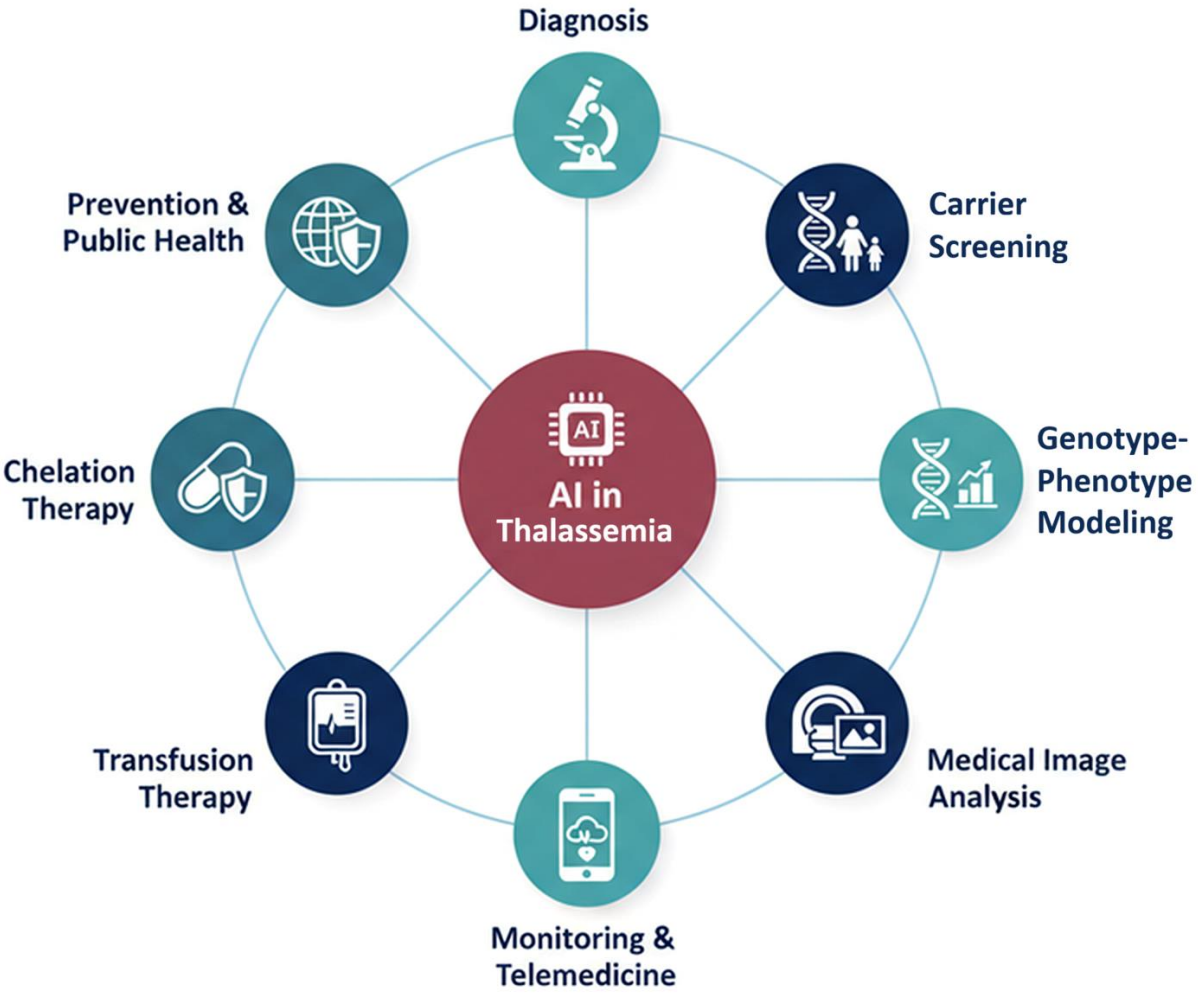

Figure 2. Main applications of artificial intelligence in thalassemia.

Main applications of artificial intelligence in thalassemia, including diagnosis, screening, genotype–phenotype modeling, image analysis, monitoring, and treatment support.

Table 2. Applications of artificial intelligence in thalassemia: opportunities and limitations

Area of application	Approaches used	Potential advantages	Main limitations	References
Diagnosis and differential diagnosis	Machine learning on routine hematologic data; Random Forest, Gradient Boosting, SVM, ANN, deep learning	Faster screening, improved distinction between thalassemia and IDA, reduced burden on specialized laboratories	Need for external validation, population differences, risk of overfitting	[21], [26-28], [29-30], [31-32], [46]
Carrier detection	Machine learning models based on complete blood count and erythrocyte indices	Large-scale preliminary screening, especially in resource-limited settings	Does not replace molecular confirmation	[26], [32-34]
Genotype-phenotype modeling	Machine learning/deep learning models, multimodal clinical data integration	Preliminary risk stratification, support for severity prediction	Limited curated datasets, complex biological relationships	[13], [21], [23], [35-36]
Medical image analysis	Deep learning, CNN, segmentation models	Automated MRI T2* assessment, standardized image analysis, blood smear image analysis	Need for standardized imaging and multicenter validation	[37-39]
Digital monitoring and telemedicine	Telemedicine platforms, EHR integration, risk models	Continuity of care, improved access, earlier recognition of deterioration	Infrastructure limitations, data privacy, digital inequality	[40-42]
Prediction of complications	Predictive machine learning models, interpretable risk models	Earlier recognition of complications and clinical deterioration	Limited clinical validation	[37], [40], [43]
Personalization of transfusion therapy	Predictive models, expert systems, machine learning	Support for transfusion-related decisions and risk estimation	Lack of validated clinical models, high cost of error	[3], [5], [16], [23], [35-36]
Personalization of chelation therapy	Machine learning models, integration of laboratory and imaging data	Potential support for regimen selection and response assessment	Lack of prospective studies, complexity of clinical decisions	[3], [5], [16], [23], [35-37]
Support for transplant-related decisions	Multimodal machine learning/deep learning models, risk stratification	Integration of genetic, clinical, and donor-related variables	High ethical and legal risks, limited validation	[16], [18], [23], [35-36]
Prevention and public health	Machine learning, XAI, population-level data analysis			

From a public health perspective, AI may be most useful when incorporated into tiered screening pathways rather than used as a standalone solution. In such a framework, routine hematologic data may serve as the first screening layer, AI-based risk stratification may identify individuals who warrant further evaluation, and confirmatory molecular testing may then be reserved for those at highest probability of carrier status. This approach could improve efficiency in high-prevalence or resource-constrained settings, where universal molecular screening may not be feasible.

At the same time, AI-based prevention strategies raise practical and ethical concerns. False-positive classifications may increase anxiety and lead to unnecessary confirmatory testing, whereas false-negative results may delay appropriate counseling or reproductive risk assessment. These risks are especially relevant when probabilistic outputs are communicated outside specialist settings. For this reason, AI-based prevention strategies should be embedded within clearly defined clinical pathways that include confirmatory testing, appropriate counseling, and oversight by trained professionals. Their performance should also be evaluated not only in terms of classification metrics, but in terms of downstream clinical and public health consequences. The real-world effectiveness of such approaches in large-scale prevention programs still requires confirmation.

Challenges and Limitations

The major barriers to broader implementation of AI in thalassemia care are summarized in Figure 3 and Table 3.

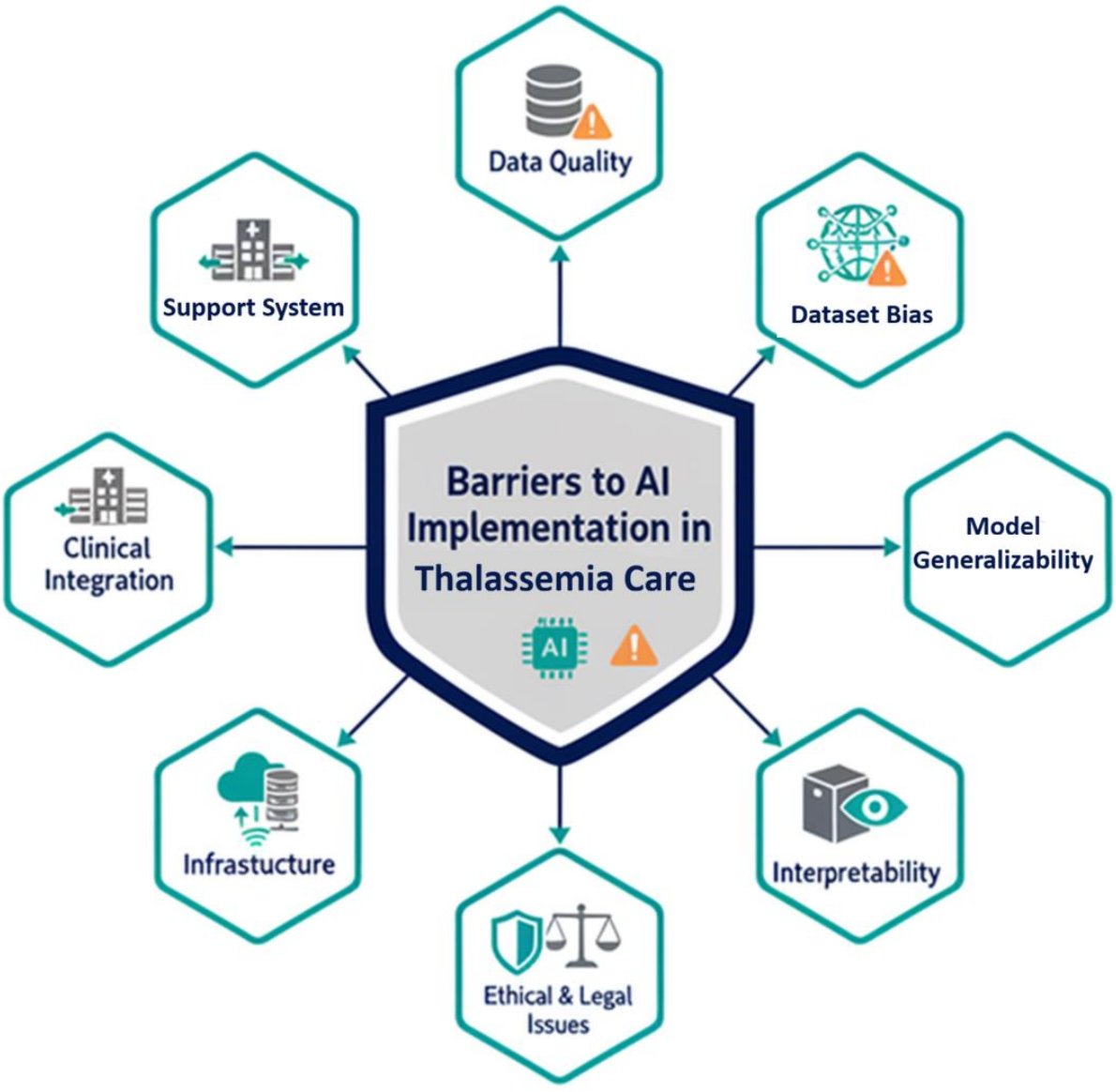

Figure 3. Major barriers to artificial intelligence implementation in thalassemia care. Key barriers to the implementation of artificial intelligence in thalassemia care, including data, methodological, ethical, and infrastructural challenges.

Despite growing interest in the application of AI to thalassemia, implementation of these technologies is accompanied by technical, methodological, ethical, and organizational constraints.

Technical and Methodological Limitations

One of the main limitations is the need for large, high-quality, and representative datasets, which is particularly difficult in genetically and clinically heterogeneous diseases [10-11,21,23]. Another challenge is the limited generalizability of models developed in a single population or center [13,21,46]. Even high-performing models may lose accuracy when applied across different laboratory settings, ethnic groups, and clinical environments.

Several additional methodological issues deserve attention. First, class imbalance may substantially affect model behavior, especially in datasets where confirmed carriers or clinically severe cases are much less frequent than controls. Second, dataset shift may occur when the characteristics of the training population differ from those of the population in which the model is ultimately applied. This may result from differences in demographic composition, local diagnostic pathways, laboratory equipment, reference ranges, or the prevalence of coexisting conditions such as iron deficiency. Third, missing data and inconsistent annotation may introduce biases that are not always apparent from headline performance metrics.

Another important limitation is the relative scarcity of prospective and multicenter validation studies. A large proportion of published work remains retrospective and proof-of-concept in design. As a result, it is often unclear whether a model that performs well under research conditions would maintain similar performance when integrated into routine clinical workflows. For translation into practice, future studies should increasingly emphasize temporal validation, external validation across centers, clinically meaningful endpoints, and transparent reporting of model development and evaluation processes. A structured overview of these barriers is provided in Table 3.

Table 3. Major barriers to the implementation of artificial intelligence in thalassemia care

Category of problem	Description	Practical significance	References
Data quality	Incomplete, heterogeneous, and non-comparable clinical, laboratory, and genetic data	Reduced model accuracy and reproducibility	10-11, 21, 46
Limited generalizability	Models developed in one population may perform worse in other settings	Restricts broader applicability	13, 21, 46
Small and imbalanced datasets	Lack of large datasets for rare subtypes and narrow clinical scenarios	Increased risk of overfitting and unstable predictions	21, 23, 46
Lack of external validation	Many models are tested only on internal datasets	Uncertain real-world clinical utility	18, 26, 29-30, 43
Limited interpretability	Complex models may be insufficiently transparent to clinicians	Reduced trust and more difficult implementation	16, 18, 23, 43
Ethical risks	Algorithmic bias, sensitivity of genetic data, opaque decision-making	Risk of unfair or difficult-to-explain outcomes	23-25
Legal and regulatory uncertainty	Lack of clear standards for AI in medicine	Slower implementation and unclear accountability	15, 23-25
Infrastructural limitations	Limited digital infrastructure, computational resources, and trained personnel	Especially critical in high-burden regions	20-21, 41, 45

Category of problem	Description	Practical significance	References
Clinical workflow integration	AI tools are often not embedded into real clinical workflows	Even good models may remain unused in practice	15-16 , 23 , 25
High cost of error	Errors in diagnosis, treatment support, or risk stratification may have serious consequen		

Many AI systems also suffer from a lack of external validation. In a considerable number of studies, models are tested only on internal datasets, making it difficult to assess their real clinical applicability [18,26,29-30,43] . In addition, the development of digital systems carries the risk of hidden technical debt, whereby accumulated architectural and organizational compromises reduce the reliability and scalability of the final solution [47].

Ethical and Legal Issues

The use of AI in medicine requires strict attention to data privacy, security, and avoidance of algorithmic bias. These issues are especially sensitive in areas involving genetic information, reproductive risk prediction, and support for high-stakes clinical decision-making [23-25] . Limited interpretability of some models may reduce clinician and patient trust and may complicate the assignment of responsibility in the event of error [16,18,43].

Infrastructural and Organizational Barriers

In many regions where thalassemia is highly prevalent, access to digital infrastructure, stable internet connectivity, computational resources, and trained personnel remains limited [20-21,41,45] . Even when technically functional algorithms are available, their integration into clinical practice requires compatibility with electronic medical systems, adaptation of clinical workflows, and staff training [15,23,25].

Federated learning is often discussed as a promising approach for distributed analysis of clinical data, but its practical implementation is also associated with technical and organizational challenges [48].

From Model Performance to Clinical Utility

A recurring issue in the AI literature is the gap between algorithmic performance and clinical usefulness. Many studies report accuracy, sensitivity, specificity, or area under the curve as primary outcomes, yet these metrics alone do not establish clinical value. A model may perform well statistically while offering limited practical benefit if it does not improve diagnostic workflow, reduce unnecessary testing, support earlier intervention, or meaningfully change patient management.

In thalassemia, clinical utility is particularly important because many AI applications are intended to function within multistep care pathways rather than as independent decision systems. For example, a screening model should ideally improve triage efficiency without increasing inappropriate referrals, and a monitoring tool should identify clinically relevant deterioration early enough to affect management. Similarly, a decision-support model for therapy personalization would need to demonstrate not only predictive performance, but also safety, reproducibility, and added benefit beyond standard expert assessment. For this reason, future work should move beyond model-centered evaluation and incorporate implementation-focused outcomes, including usability, workflow integration, clinician acceptance, and impact on patient care.

Clinical Implications for Healthcare Practice

Current applications of artificial intelligence in thalassemia remain largely supportive rather than autonomous. Clinicians should interpret AI-generated outputs as decision-support tools rather than replacements for clinical judgment.

Potential near-term applications include:

- automated differentiation between thalassemia trait and iron deficiency anemia,
- prediction of transfusion requirements,
- monitoring of iron overload through imaging analytics,
- enhancement of screening programs in underserved regions.

However, integration into routine practice requires validation across diverse populations and healthcare environments.

The evolution of AI applications in thalassemia reflects broader transformations occurring across modern medicine, where data-driven tools increasingly complement traditional clinical expertise. Lessons learned from thalassemia may inform digital transformation strategies in other chronic hematologic and genetic disorders.

Future Perspectives

Future applications of AI in thalassemia are likely to develop along several lines. First, the advancement of explainable AI will be particularly important, as it may improve interpretation of model outputs and strengthen trust in algorithm-assisted clinical decisions [43]. This is especially relevant in scenarios where AI may influence diagnostic or therapeutic reasoning.

Second, further development of personalized medicine approaches can be expected, in which AI integrates clinical, laboratory, genetic, and imaging data to support individualized monitoring and management [23,35-36,49]. Third, the integration of AI with omics technologies remains of interest, as it may contribute to a deeper understanding of thalassemia pathophysiology and refinement of genotype-phenotype relationships [13,44].

Further expansion of telemedicine and digital monitoring may also improve access to specialized care, particularly in resource-limited settings, provided that adequate infrastructure and regulatory support are available [40-42]. However, all of these directions require clinical validation, standardization, and assessment of their impact on real-world outcomes before broader routine adoption can be justified.

Conclusion

Artificial intelligence and digital technologies are expanding the possibilities for the diagnosis, monitoring, and prevention of thalassemia. The most advanced applications are currently observed in the analysis of routine hematologic data, differential diagnosis of microcytic anemias, carrier detection, and medical image analysis. These approaches have demonstrated promising performance in controlled settings and may improve diagnostic accessibility and screening efficiency, particularly in resource-limited environments. In contrast, applications related to therapy personalization, transplant decision support, and complex genotype–phenotype modeling remain largely investigational.

Despite encouraging progress, significant barriers limit the translation of artificial intelligence into routine clinical practice. These include limited availability of large and representative datasets, insufficient external validation, challenges related to model interpretability, and difficulties in integration into clinical workflows. Ethical and regulatory considerations further complicate implementation, particularly in the context of genetic data and high-stakes decision-making. Therefore, artificial intelligence should currently be regarded as a supportive tool rather than a replacement for clinical expertise. Its future role in thalassemia care will depend on rigorous validation, standardization, and demonstration of meaningful clinical utility in real-world settings.

DECLARATIONS

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

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