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Review Article

Aging with Thalassemia and Sickle Cell Disease: A Gerontological Model of Accelerated Multimorbidity and Function-Centered Care Beyond Midlife

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Abstract. ***Background:*** **Thalassemia and sickle cell disease are now increasingly present as lifelong chronic conditions in high-income countries, with growing numbers of patients reaching their 50s and 60s. This demographic shift transforms hemoglobinopathies from childhood-threatening disorders into chronic, multisystem conditions with cumulative morbidity. However, data specifically focused on later-life hemoglobinopathy populations remain limited, fragmented, and often extrapolated from younger cohorts, leaving hematologists and internists relatively unprepared for the functional decline, vulnerability, and geriatric syndromes that can characterize later life in these populations.**
Content**: This expert opinion narrative review synthesizes available evidence on the intersection of disease-driven pathology (anemia, hemolysis, vasculopathy), long-term treatment burden (transfusion-related iron overload, chelation toxicities), and aging biology (declining physiologic reserve, sarcopenia, cognitive vulnerability) in adults beyond midlife. Given the historical survival patterns in hemoglobinopathies and the inconsistent definition of "older adult" across studies, particularly in sickle cell disease, we use a pragmatic age threshold of >=50 years for the main gerontological framing, while incorporating evidence from cohorts beginning at 40-49 years when that is how the literature defines older hemoglobinopathy populations. We distinguish disease-**

specific priorities: thalassemia faces myocardial and hepatic iron deposition and endocrine failure, while sickle cell disease confronts cerebrovascular disease, chronic pain, and cardiopulmonary complications. Critically, care targets in later life must extend beyond survival and organ-specific metrics to functional endpoints, disability prevention, cognitive health, and quality of life. A conceptual mapping links mechanisms of hemoglobinopathy to established gerontology constructs, including inflammaging, cellular senescence, and vascular aging, while acknowledging that direct mechanistic evidence in older hemoglobinopathy cohorts remains incomplete.

***Conclusions*: Three adjustments are necessary in adults beyond midlife: monitoring should prioritize early detection of treatable complications and emerging functional impairment rather than only documenting cumulative organ damage; therapeutic decisions should weigh treatment benefit, treatment burden, comorbidity burden, and goals of care rather than defaulting to pediatric-era protocols; and care systems should embed shared decision-making, palliative principles, and multidisciplinary coordination within primary care networks, with specialist hemoglobinopathy centers functioning as disease-specific hubs rather than stand-alone primary care providers.**

Keywords: Hemoglobinopathies; Thalassemia; Sickle Cell Disease; Aging; Multimorbidity; Frailty; Geriatric Assessment; Chronic Disease.

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Introduction. Aging and Hemoglobinopathy Survivorship as a Gerontological Challenge. Until the 1980s, many children with transfusion-dependent thalassemia or severe sickle cell disease died before adulthood. Improvements in blood banking, iron chelation therapy, and preventive care fundamentally altered the disease course.[1,2] Survival has improved substantially, and in high-income countries with organized access to comprehensive care, an increasing number of patients now reach midlife and beyond, creating a new clinical challenge: the long-term management of aging adults living with lifelong hemoglobin disorders.[2]

This improvement is not uniform globally. The present manuscript primarily addresses patient populations in high-income settings where longitudinal transfusion programs, iron monitoring, disease-modifying therapies, and multidisciplinary specialty access are feasible. In many low- and middle-income settings, early mortality, limited access to safe transfusion and chelation, infectious complications, and constrained diagnostic infrastructure remain dominant determinants of outcomes, and the clinical priorities and feasible monitoring strategies may differ considerably.[3]

Adults with hemoglobinopathies experience a qualitatively different disease burden, not dominated by acute crises alone, but by cumulative organ damage, polypharmacy, and the convergence of disease-specific complications with age-associated chronic disease. This phenotype, premature multimorbidity combined with a lifelong genetic disease burden, makes hemoglobinopathies a potential model for studying health-span compression in chronic illness.[4]

Gerontology is the scientific study of the processes and problems of aging from biological, clinical, psychological, and social perspectives. In this manuscript, gerontological constructs refer to established conceptual models in gerontology used to explain vulnerability in later life, such as frailty, inflammaging, and loss of physiologic reserve, and a gerontological model refers to a clinical framework that prioritizes function, cognition, disability prevention, and quality of life, integrating disease-specific pathology with age-related vulnerability.[5] This is distinct from normal aging in the general population: the framework does not assume that hemoglobinopathy survivors are simply older, but rather that cumulative disease injury and decades of therapy can produce geriatric syndromes

and loss of reserve at younger chronological ages than typically seen in unselected populations.

For this review, beyond midlife is intentionally pragmatic. We focus primarily on patients aged >=50 years, the phase when cumulative organ complications, multimorbidity, and functional vulnerability are increasingly likely to intersect, and when goal-based decision-making becomes essential. However, we also incorporate evidence from cohorts beginning at 40-49 years because older-adult definitions in sickle cell disease literature frequently begin at age 40, reflecting historical survival patterns and earlier accumulation of organ damage. We identify three mechanistic factors contributing to morbidity: disease-related pathology, treatment-related burdens, and biological and functional aging. This triad framework separates mechanisms that require different interventions and clarifies which clinical problems reflect age per se versus cumulative disease and treatment exposure.

Methodological Approach. This manuscript represents an expert opinion narrative review informed by a structured literature search, recognizing that prospective data on aging hemoglobinopathy populations remain limited and that many recommendations are necessarily based on observational cohorts, registries, and guideline extrapolation.

We conducted a structured search of PubMed, Scopus, and Web of Science for studies published between 2000 and 2025. Search terms included combinations of thalassemia, sickle cell disease, aging, older adult, frailty, multimorbidity, functional decline, quality of life, and geriatric assessment. Priority was given to cohort studies, clinical guidelines, registry data, and systematic reviews relevant to adult and aging populations. We also reviewed reference lists of key articles to identify additional studies.

Inclusion criteria emphasized studies reporting outcomes or clinical characteristics in adult populations with explicit age stratification, preferably >=50 years and >=40 years when older-adult stratification began at that threshold. Exclusion criteria included pediatric-only studies without adult data, studies without age-stratified outcomes, and reports limited to isolated case descriptions when they did not inform broader clinical patterns.

In total, 52 publications informed the narrative synthesis. Because the literature is heterogeneous and this review was not designed as a formal systematic review, study selection is summarized narratively in the main text. A detailed summary of the search strategy, study selection rationale, study characteristics, and reasons for exclusion at full-text review is provided in the Supplementary File (**Supplementary Table S1**).

Definitions: Genotypes, Clinical Phenotypes, and Terminology. Throughout the manuscript, thalassemia refers to inherited disorders of reduced globin chain synthesis, including alpha-thalassemia, beta-thalassemia, and delta-beta-thalassemia. Genotype and modifier effects, including co-inheritance of alpha-thalassemia, HbE, or fetal hemoglobin-modulating variants, contribute to a spectrum of severity.[6,7]

We use contemporary phenotype-based terminology when possible. Transfusion-dependent thalassemia refers to thalassemia requiring regular lifelong transfusion to survive and maintain adequate hemoglobin levels; non-transfusion-dependent thalassemia refers to thalassemia not requiring regular transfusions for survival but still associated with chronic anemia and significant long-term complications. Traditional terms such as thalassemia major and thalassemia intermedia are sometimes retained in the literature and are broadly aligned with these phenotypes, but do not fully capture clinical variability.[7,8]

Sickle cell disease refers to hemoglobin S-associated genotypes characterized by chronic hemolysis and vaso-occlusion, including HbSS and compound heterozygous forms such as HbSC and HbS/beta-thalassemia.[9] When clinical points apply predominantly to one subgroup, this is stated explicitly to avoid ambiguity (**Table 1**).

Hemoglobinopathy Pathology and Gerontological Constructs. Hemoglobinopathies intersect with several biological pathways widely implicated in aging and age-related disease, including chronic low-grade inflammation, cellular senescence, and vascular aging. In classic gerontology, inflammaging refers to age-associated increases in pro-inflammatory signaling that contribute to organ dysfunction and increased vulnerability.[10]

In hemoglobinopathies, chronic hemolysis, recurrent ischemia-reperfusion injury, transfusion exposure, and chronic pain syndromes can sustain inflammatory activation that may resemble inflammaging even at younger chronological ages, plausibly accelerating loss of physiologic reserve.

Similarly, cellular senescence is a hallmark of aging biology and has been proposed as a mechanistic contributor to functional decline.[11] While accelerated aging signatures have begun to be described in sickle cell disease, direct causal pathways linking molecular aging markers to clinical geriatric syndromes in older hemoglobinopathy cohorts remain incompletely established, and mechanistic claims should be interpreted cautiously.[12]

The overlap is clinically useful when used as a framework rather than a deterministic explanation. In thalassemia, long-term transfusion and iron overload can lead to cumulative oxidative stress and direct tissue injury, which may reduce organ reserve in the

Table 1. Genotype, carrier states, and clinical classification in thalassemia and sickle cell disease.

Category	Term / Genotype	Applies to	Working definition / Clinical relevance
Genotype (disease-causing)	β^0/β^0 (e.g. CD39/CD39)	β-thalassemia	Absent β-globin production; severe anemia; typically transfusion-dependent
Genotype (disease-causing)	β^0/β^+ (e.g. CD39/IVS-I-110)	β-thalassemia	Reduced β-globin production; moderate to severe phenotype
Genotype (disease-causing)	β^+/β^+ (e.g. IVS-I-110/IVS-I-6)	β-thalassemia	Mild to moderate reduction in β-globin synthesis
Genotype (carrier / trait)	β/β^0	β-thalassemia	β-thalassemia trait (carrier state), usually asymptomatic or mild anemia
Genotype (carrier / trait)	β/β^+	β-thalassemia	Mild carrier phenotype with minimal clinical expression
Genotype (carrier / trait)	δβ-thalassemia trait	Thalassemia	Reduced δ- and β-globin synthesis with elevated HbF; usually mild phenotype
Genotype (carrier / trait)	α^0 (--/αα)	α-thalassemia	Deletion of two α-globin genes; α-thalassemia trait
Genotype (carrier / trait)	α^+ (-α/αα)	α-thalassemia	Single α-globin gene deletion; mild carrier state
Clinical classification	TDT (Transfusion-Dependent Thalassemia)	β-thalassemia	Requires regular lifelong transfusions for survival
Clinical classification	NTDT (Non-Transfusion-Dependent Thalassemia)	β-thalassemia	Does not require regular transfusions but associated with chronic anemia
Hematological phenotype	β^0/β^0	β-thalassemia	Severe anemia, ineffective erythropoiesis
Hematological phenotype	β^0/β^+	β-thalassemia	Intermediate to severe anemia
Hematological phenotype	β^+/β^+	β-thalassemia	Mild to moderate anemia
Genotype	HbSS	Sickle cell disease	Homozygous HbS; severe hemolysis and vaso-occlusive disease
Genotype	HbSC	Sickle cell disease	Compound heterozygous HbS/C; usually milder phenotype
Genotype	HbS/β-thalassemia (β^0 or β^+)	Sickle cell disease	Combined HbS and β-thal mutation; variable severity depending on mutation

Note: TDT and NTDT represent clinical classifications rather than true biological phenotypes, which are determined by the underlying β-globin genotype.

gerontological sense, lowering tolerance to acute illness, surgery, or medication changes. In sickle cell disease, recurrent vaso-occlusion and hemolysis can cause microvascular injury and endothelial dysfunction that parallels conceptual models of vascular aging, potentially amplifying risk when traditional cardiovascular risk factors emerge in midlife and later life.[13,14]

This section, therefore, supports a functional thesis: regardless of whether hemoglobinopathy injury is labeled accelerated aging, decades of disease activity and therapy exposure can produce phenotypes that resemble geriatric multimorbidity, including frailty, polypharmacy, cognitive vulnerability, and disability, earlier than expected by chronological age alone.

Functional Status, Frailty, and Quality of Life: The New Clinical Target. For decades, hemoglobinopathy care pivoted on a single metric: survival. Preventing death from acute chest syndrome, stroke, or cardiac decompensation was and remains essential. But a longer life without functional capacity is clinically hollow.

Contemporary aging research demonstrates that functional status, not chronological age, predicts outcomes in chronic illness. Adults aging with hemoglobinopathies may exhibit functional decline, including weakness, slow gait, low activity, exhaustion, and weight loss, that overlaps with frailty syndromes in gerontology. Frailty remains under-recognized in hemoglobinopathy clinics because hematology practice is traditionally oriented toward organ-specific complications and crisis prevention rather than functional trajectories.[15]

Quality of life, cognitive function, employment, and intimate relationships are outcomes that matter profoundly to patients. Older adults with sickle cell disease describe the paradox of longer survival accompanied by persistent pain, fatigue, stigma, and loss of independence. Thalassemia cohorts report a similar tension between improved survival and the burden of endocrine, cardiac, and treatment-related complications that accumulate across decades. Functional and psychosocial endpoints must therefore be systematized in later-life hemoglobinopathy care, not treated as optional adjuncts.

For patients aged >=50 years, and earlier when functional concerns emerge, annual surveillance should include physical function, cognitive screening, depression and anxiety screening, social engagement, and employment or role status. Frailty screening tools should be incorporated, and if weakness is recognized, referral to physical medicine, geriatrics, rehabilitation, or

structured exercise programs becomes urgent.[16,17] This conceptual framework is illustrated in **Figure 1**.

Treatment And Follow-Up Evolve With Age: Balancing Benefit, Burden, And Reserve. As patients move beyond midlife, hemoglobinopathy treatment is rarely a simple continuation of pediatric-era targets. What changes is not only the accumulation of complications, but also the balance between treatment benefit and treatment burden in the context of multimorbidity, declining renal clearance, polypharmacy, and shifting patient priorities.

In thalassemia, transfusion and chelation remain foundational, but the clinical question increasingly becomes how to sustain function and prevent irreversible decline while minimizing long-term toxicities. Volume tolerance, diastolic dysfunction, arrhythmias, and chronic kidney disease complicate transfusion delivery and may require slower transfusion protocols, individualized diuretic strategies, and closer monitoring of cardiac status. Chelation strategy often needs to evolve as renal impairment, hearing, and vision issues develop, and cumulative adherence fatigue can mandate dose adjustments, agent changes, or deliberate de-intensification when the competing risks and patient goals indicate diminishing marginal benefit.[18,19]

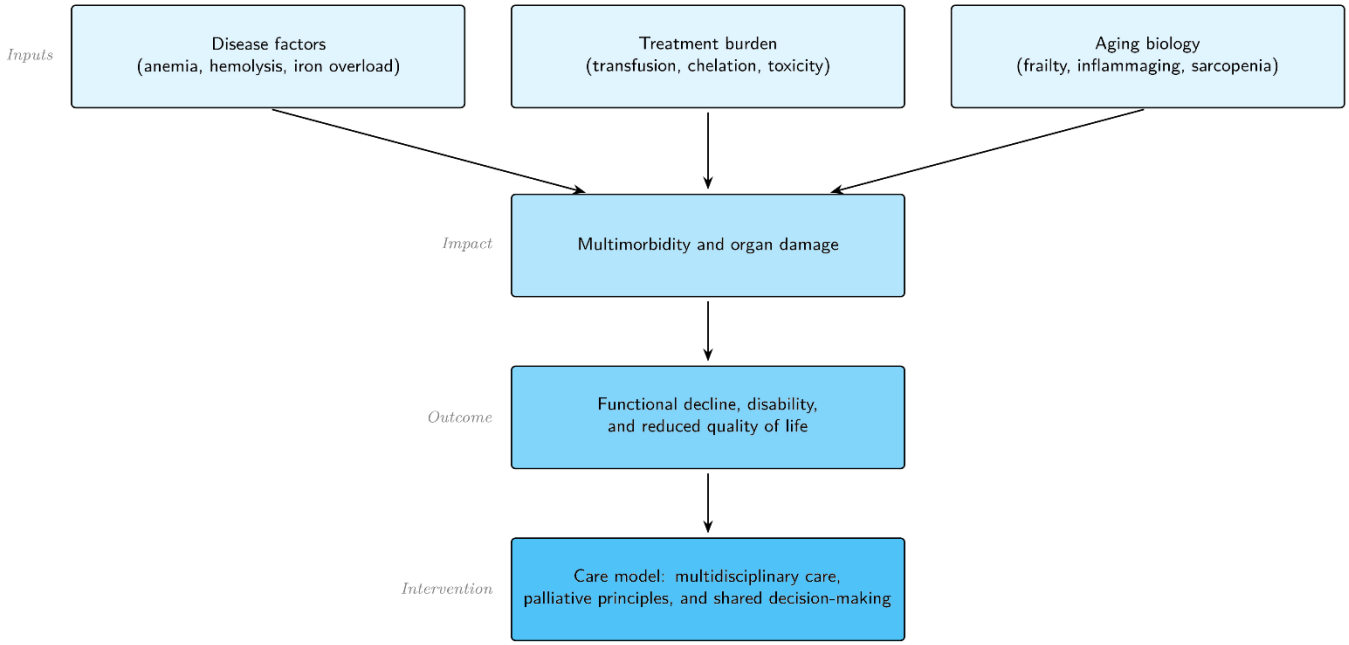

Figure 1. Conceptual model of aging in hemoglobinopathies. Disease-related factors, treatment burden, and biological aging interact to drive multimorbidity and organ damage, leading to functional decline and reduced quality of life, and supporting the need for a multidisciplinary, function-centered care model incorporating palliative principles and shared decision-making.

In sickle cell disease, major disease-modifying approaches, including hydroxyurea, transfusion-based strategies, and newer therapies, have been studied predominantly in younger cohorts, and older adults have historically been underrepresented in trials.[12] Beyond midlife, hydroxyurea dose titration may be constrained by renal function, marrow reserve, infection risk, and concomitant medications.[20] Transfusion decisions also increasingly intersect with comorbidity burden, alloimmunization history, and venous access complications.[21] In this setting, proactively defining realistic endpoints, including pain interference, mobility, cognitive stability, work capacity, and time spent outside the hospital, is often more meaningful than escalating therapy intensity by default.

Beyond age 50, the clinical unit of care should shift from reactive specialist visits to a planned annual comprehensive review that integrates organ surveillance with functional and psychosocial assessment. This visit should explicitly revisit goals of care, treatment tolerance, competing risks, and patient priorities, and should end with a written plan shared with primary care and key specialists.

Emerging Morbidities in Aging Hemoglobinopathies: The Disease-Driven and Treatment-Driven Triad. The spectrum of complications in hemoglobinopathy survivors reflects both disease-specific mechanisms and the cumulative effects of chronic treatment exposure. Importantly, many complications discussed below are not exclusive to later life: stroke, pulmonary complications, endocrine dysfunction, and pain can appear across the lifespan. What changes beyond midlife is the cumulative prevalence and severity of organ

damage, the rising burden of age-associated comorbidities, and the decline in physiologic reserve that converts apparently stable disease into vulnerability to disability.[22]

Major organ system complications in thalassemia and sickle cell disease are summarized in **Tables 2** and **3**.

Cardiovascular complications and the paradox of iron. Cardiopulmonary disease is a major determinant of morbidity and mortality in both thalassemia and sickle cell disease, but the dominant mechanisms differ substantially.

In thalassemia, myocardial iron overload accumulates quietly, driven by transfusion burden and chelation adequacy. Iron-laden cardiomyocytes develop restrictive or dilated phenotypes; arrhythmias emerge as late, sometimes fatal complications. Cardiac MRI T2* remains central to monitoring and should not be replaced by ferritin alone.[23,24]

In sickle cell disease, cardiac strain more often reflects chronic anemia and hemolysis physiology, microvascular dysfunction, and cardiopulmonary disease, including pulmonary hypertension, rather than transfusional iron alone, except in those receiving long-term transfusions. Diastolic dysfunction is common, and the clinical impact is amplified when hypertension, diabetes, and kidney disease emerge beyond midlife.[25,26]

Elevated tricuspid regurgitant jet velocity on echocardiography is common in both conditions, but screening echocardiographic markers must be distinguished from hemodynamically confirmed pulmonary hypertension. In sickle cell disease, pulmonary hypertension is strongly associated with mortality risk. In thalassemia cohorts, elevated tricuspid regurgitant jet velocity has also been reported and may reflect complex cardiopulmonary physiology.

Clinical overview. Echocardiography remains a reasonable periodic screening tool in adults and should be interpreted in the context of age, symptoms, and comorbidities. In patients beyond midlife, escalation of monitoring frequency is most defensible when new symptoms, abnormal diastolic parameters, elevated

Table 2. Comparative overview of major complications in later-life thalassemia and sickle cell disease.

Clinical domain	Thalassemia	Sickle cell disease	Why aging changes the picture
Cardiovascular	Myocardial iron overload, arrhythmias, restrictive/dilated cardiomyopathy	Pulmonary hypertension, diastolic dysfunction, chronic anemia-related cardiac strain	Comorbid hypertension, diabetes, and CKD reduce physiologic reserve
Liver	Iron overload, fibrosis, cirrhosis, viral hepatitis	Inflammation-related liver injury; transfusional iron in selected patients	Metabolic liver disease and malignancy risk increase with age
Endocrine / bone	Hypogonadism, diabetes, thyroid/parathyroid dysfunction, osteoporosis	Diabetes risk, hypogonadism, low bone density	Leads to sarcopenia, falls, fractures, and frailty
Renal	Tubular dysfunction, CKD, chelation-related nephrotoxicity	Albuminuria, CKD, papillary necrosis	Alters drug clearance and increases cardiovascular risk
Neurologic	Vascular brain injury (especially NTDT), cognitive changes	Silent infarcts, overt stroke, cognitive decline	Age-related vascular risks amplify disease-specific injury
Pain / function	Fatigue, musculoskeletal limitation	Chronic pain, osteonecrosis, opioid burden	Functional decline and disability become dominant outcomes

Note: The two conditions differ fundamentally in pathophysiology; comparison is presented for clinical orientation only.

Table 3. Suggested comprehensive monitoring framework for adults ≥50 years with hemoglobinopathies.

Domain	Assessment	Timing	Clinical trigger / action
Function / frailty	Gait speed, grip strength, FRAIL screen	Annually	Decline → refer to rehabilitation / geriatrics
Cognition / mood	Cognitive screen (MoCA), depression/anxiety screening	Annually or if concern	Impairment → neuropsychology / mental health referral
Cardiovascular	Echocardiography; cardiac MRI T2* (thalassemia); BP control	Annual review	Abnormal findings → cardiology referral / adjust therapy
Liver	MRI iron or elastography; hepatitis screening	Risk-based	Fibrosis/cirrhosis → hepatology referral; consider HCC surveillance
Endocrine / bone	Glucose, thyroid, gonadal function, vitamin D, DXA	Annual; DXA periodically	Abnormal → endocrine treatment; fracture prevention strategies
Renal	eGFR, albuminuria, medication review	At least annually	Albuminuria/decline → nephrology referral; adjust drugs
Neurologic	Clinical history, cognitive review ± imaging	Annual	Symptoms or decline → brain imaging / neurology referral
Pain / QoL	Pain interference, sleep, function, social support	Every visit; formal annual review	Disability or poor QoL → multidisciplinary pain / palliative care

tricuspid regurgitant velocity, or cardiovascular risk factors emerge. For thalassemia, cardiac MRI T2* should remain central in patients with significant transfusion burden or prior abnormal results. When pulmonary hypertension is suspected, right heart catheterization is required to define the mechanism and guide therapy.[27,28]

Complex combined pathology: hepatic fibrosis, iron overload, and metabolic liver disease. Liver iron concentration predicts morbidity and interacts with long-term outcomes. Yet in aging patients, at least two distinct pathologies may coexist: iron-driven fibrosis or cirrhosis and metabolic fatty liver disease.[29]

Iron overload and hepatic fibrosis are common in heavily transfused patients. Duration of iron overload, not just peak levels, appears clinically relevant. MRI-based liver iron quantification is generally preferred when available, particularly because inflammation and vascular congestion may complicate elastography interpretation.[30,31]

Metabolic-associated fatty liver disease is increasingly recognized among older patients with hemoglobinopathies and can coexist with iron overload. Distinguishing iron-driven from metabolic disease is clinically critical: iron disease demands chelation optimization; metabolic disease benefits from weight management, exercise, and metabolic control. Both can increase hepatocellular carcinoma risk. In cohorts transfused before modern viral screening, hepatitis C exposure remains common.[33,34,32]

Clinical overview. Liver surveillance should remain disease-specific, but beyond midlife, the stakes of cumulative fibrosis and malignancy risk become more consequential. Hepatitis B and C status should be assessed; a hepatology referral should follow evidence of advanced fibrosis; and hepatocellular carcinoma surveillance should be maintained when cirrhosis is present.

Diabetes, hypogonadism, sarcopenia, and bone loss. Endocrine dysfunction is common in older thalassemia patients, often reflecting decades of iron exposure, and also occurs in sickle cell disease. Iron deposition in pancreatic beta cells impairs insulin secretion, while hepatic iron and systemic inflammation amplify insulin resistance.[35]

Hypogonadotropic hypogonadism is a frequent endocrinopathy in thalassemia and contributes to sexual dysfunction, infertility, bone loss, and frailty.[36,37] Hypogonadism in sickle cell disease is less systematically documented and may be underrecognized. Thyroid and parathyroid disease are also common.[38]

Osteoporosis and sarcopenia are especially important beyond midlife because they convert chronic disease burden into falls, fractures, and loss of independence. The key issue in older adults is not simply detecting endocrinopathies but preventing functional consequences.[39]

Clinical overview. Screening for diabetes, thyroid dysfunction, gonadal dysfunction, calcium and vitamin D status, and bone density should be individualized by phenotype, transfusion exposure, symptoms, and age. Beyond age 50, the emphasis should shift from endocrine diagnosis alone to preservation of mobility, fracture prevention, and rehabilitation.

Renal impairment: drug clearance, imaging, and cardiovascular protection. Chronic kidney disease is an important emerging morbidity in aging hemoglobinopathy populations. Mechanisms differ by condition: vaso-occlusive injury and papillary necrosis in sickle cell disease; iron-related and anemia-related tubular dysfunction in thalassemia; and chronic hemolysis-associated tubular injury in both. Albuminuria is common and clinically meaningful.[40,41]

Renal impairment alters drug clearance and toxicity risk. A chelation strategy may need adjustment, imaging choices may be constrained, and hypertension and diabetes management become more urgent, as these risks compound hemoglobinopathy-related renal vulnerability.[42,43,44]

Clinical overview. Annual screening for albuminuria and glomerular filtration rate is reasonable in adulthood and becomes more consequential beyond midlife. Nephrology referral is appropriate for persistent albuminuria or reduced glomerular filtration rate, particularly when therapy adjustments are required.

Brain decline: stroke, silent infarction, and processing-speed loss. Cerebrovascular disease is a hallmark of sickle cell disease but can be under-recognized in adult practice. Overt stroke and silent cerebral infarction accumulate with age and interact with traditional vascular risk factors. Cognitive impairment is prevalent but often missed unless specifically assessed.[45,46,47]

In thalassemia, overt stroke is less typical, but vascular brain injury has increasingly been described, particularly in non-transfusion-dependent disease. Cognitive effects in thalassemia remain less well studied and probably heterogeneous.[48]

Clinical overview. Beyond midlife, cognitive screening becomes more clinically actionable because cognitive vulnerability interacts strongly with adherence, employment, driving safety, medication burden, and independent living. In adults with sickle cell disease, especially those with prior neurologic symptoms, hypertension, or functional decline, brain imaging may inform risk stratification, although evidence for universal adult MRI screening remains limited, and practice varies by setting.

Disability, opioid management, and chronic pain: a functional endpoint. In older adults, the approach to pain management should focus on functional outcomes rather than just pain scores.[49,50] Unlike acute vaso-occlusive crises, chronic baseline pain does not respond reliably to transfusions or hydroxyurea and often reflects mixed nociceptive, neuropathic, and centrally amplified mechanisms.[51] Osteonecrosis may become a dominant cause of reduced mobility.

Quality of life and functional status correlate strongly with pain interference and depression. These outcomes must be addressed directly, rather than inferred from hemoglobin values or hospital utilization alone.[52]

Clinical overview. Pain management in later life should be defined by functional endpoints rather than pain scores alone. Multimodal pain management, including non-opioid strategies, physical therapy, psychological interventions, and palliative-informed approaches, should be prioritized. In patients with progressive disability or severe symptom burden, palliative care consultation is appropriate even years from the end of life.

Remaining complications: pulmonary, thrombotic, infectious, and mental health. Pulmonary complications are a leading cause of morbidity and mortality in sickle cell disease and thalassemia patients, and cardiac iron overload or pulmonary hypertension are also risks. Chronic lung disease and obstructive sleep apnea are increasingly recognized but under-screened.[53,54,55,56] Venous thromboembolism risk is elevated, particularly in splenectomized patients or those with advanced kidney disease.[57,58] Infection risk and transfusion-related alloimmunization remain ongoing concerns.[59]

Depression and anxiety are highly prevalent. Stigma, discrimination, and social isolation compound psychological burden, particularly in older populations. Routine screening for depression and anxiety should be incorporated into later-life hemoglobinopathy care.[60]

Preventive Care and Shared Decision-Making in Older Age. Adults with hemoglobinopathies often receive inconsistent routine preventive care despite increasing survival into late adulthood in high-income settings. Barriers include crowded hematology schedules, lack of coordination between specialties, and assumptions that hemoglobinopathy-related risk dominates all other health priorities.

Beyond age 50, clinicians should explicitly discuss preventive care goals and align them with life expectancy, functional status, and patient values. Preventive care decisions should be integrated into shared decision-making rather than occurring by default or omission. Hematology visits should not replace primary care but should reinforce coordination with primary care for cancer screening, cardiovascular risk management, vaccinations, bone health, and routine preventive services.[61]

Organizing Multidisciplinary Care: Principles For Complex Chronic Illness. Ideal multidisciplinary care involves hematologists, cardiologists, endocrinologists, hepatologists, nephrologists, neurologists, pulmonologists, pain specialists, psychologists, physical and occupational therapists, social workers, and pharmacists. Nevertheless, few centers can sustain all specialties on-site.[62]

A pragmatic gerontology-informed model designates a hematology nurse coordinator or case manager as the hub: this person knows each patient, coordinates referrals, follows up on test results, and serves as the point of contact for patient questions. This is consistent with chronic care models and published standards emphasizing shared care arrangements among specialist centers, local hospitals, and primary or community care teams.

Specialized hemoglobinopathy centers should not function as the patient's de facto primary care provider. The most sustainable model in high-income settings is shared care: the specialist center serves as the disease-specific hub, responsible for hemoglobinopathy-directed management and coordinating multidisciplinary input, while primary care delivers routine preventive care and general chronic disease management, with clear communication and rapid re-access pathways to specialist expertise.[63]

The comprehensive annual review beyond midlife should integrate functional and psychosocial assessment, treatment tolerability review, medication review, and organ monitoring tailored to age, phenotype, and medical history. Shared decision-making should include explicit discussion of care goals, competing risks, the expected benefits versus burdens of interventions, and treatment acceptability.

Integrating Palliative Principles: A Shift in Clinical Mindset. Palliative care should not be confused with end-of-life care. This approach improves quality of life and functional status by addressing symptom burden, clarifying goals, and aligning medical interventions with patient values throughout all stages of disease.

In older patients with hemoglobinopathy, this shift is particularly important because the dominant clinical threats often become pain interference, fatigue, disability, mood disorders, and caregiver burden, even when organ metrics appear stable. Standard hematology protocols may provide limited benefit if they do not address pain, mood, sleep, and social functioning.

Early palliative consultation, not triggered by crisis, provides patients and families with structured discussions regarding priorities, realistic expectations, and decision-making under competing risks. Palliative

principles, including shared decision-making, goal clarification, symptom optimization, and psychosocial support, should be embedded in routine hemoglobinopathy care rather than reserved for late-stage scenarios.[63,64]

Research Priorities and Future Directions. Three critical gaps must be addressed.

Prospective aging cohorts. Long-term studies of adults beyond midlife with thalassemia and sickle cell disease, incorporating standardized measures of frailty, cognition, disability, quality of life, and functional decline, are essential.

Interventional trials. Evidence-based trials of frailty reduction, sarcopenia management, cognitive rehabilitation, structured pain interventions, and psychosocial support remain limited. Trials should prioritize patient-reported outcomes and disability prevention alongside organ metrics and mortality.

Shared decision-making tools and care-delivery research. Monitoring strategies that integrate organ surveillance with functional assessment need evaluation, including comparative effectiveness of shared-care models, nurse navigation, telemedicine-supported specialty access, and multidisciplinary clinic structures across diverse health systems.

Conclusions. Three changes in clinical perspective are necessary as hemoglobinopathy patients move beyond midlife, particularly in high-income settings where survival into the 50s and beyond is increasingly common.

Monitoring must evolve. The goal is not only to record cumulative damage but to detect treatable complications early and identify modifiable functional impairment. Beyond age 50, and earlier when clinical vulnerability emerges, routine assessments should include gait speed, grip strength, cognitive screening, depression screening, frailty screening, and social functioning.

Therapeutic decisions must weigh complexity. Blind adherence to pediatric-era protocols becomes ineffective in aging patients with polypharmacy, multiple organ involvement, and limited reserve. Shared decision-making should incorporate comorbidity burden, treatment acceptance, organ reserve, realistic benefit, and patient goals.

Care systems must integrate palliative principles and multidisciplinary coordination. Shared-care models in which specialist hemoglobinopathy centers function as disease-specific hubs, coordinating with primary care and local services, are more defensible than expecting specialist centers to replace primary care.

Hemoglobinopathies, as models of cumulative multimorbidity in lifelong genetic disease, offer gerontology both a clinical challenge and an opportunity. The survivors of these disorders demand that we move beyond pediatric emergency medicine and hematological metrics, and embrace the gerontological imperative: optimize function, prevent disability, clarify goals, alleviate suffering, and support the lived experience of growing old with chronic, complex, systemic disease.

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