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Co-inherited α-Thalassemia and β-Globin Haplotypes as Determinants of Vaso-Occlusive Crisis, Stroke, and Mortality in Sickle Cell Disease: A Systematic Review

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ABSTRACT

Background: Clinical severity in sickle cell disease (SCD) varies widely. Co-inherited α-thalassemia and β-globin (HBB) haplotypes are proposed modifiers, but their relationships with vaso-occlusive crisis (VOC), stroke, and mortality remain uncertain.

Objectives: To synthesize evidence on the associations of α-thalassemia and β-globin haplotypes with VOC, cerebrovascular outcomes, and mortality in SCD.

Methods: We conducted a PRISMA-guided systematic review (final search 6 Nov 2025) across MEDLINE, Embase, Web of Science, CENTRAL, Scopus, Google Scholar, and regional/grey sources. Eligible studies enrolled individuals with SCD (any genotype/age) and reported genotyped α-thalassemia and/or β-globin haplotypes alongside ≥1 prespecified outcomes. Two reviewers screened records, extracted data, and appraised risk of bias.

Results: Of 1,964 records, 10 studies met inclusion (predominantly pediatric HbSS; Caribbean, South America, North America, and French Guiana). Across cohorts, α-thalassemia showed a consistent protective signal for cerebrovascular phenotypes: lower odds of overt stroke and fewer abnormal transcranial Doppler velocities. Evidence for VOC was heterogeneous—one prospective cohort reported higher healthcare-attended VOC in homozygous α-thalassemia, whereas adjusted analyses elsewhere were null. Mortality data were scarce; a cross-sectional genetic survey suggested better survival among α-thalassemia carriers. β-globin haplotypes showed weak or inconsistent associations with all outcomes once fetal hemoglobin and treatment era were considered. The principal methodological limitation was residual confounding; outcome measurement for stroke/TCD was robust, while VOC ascertainment varied.

Conclusions: α-thalassemia appears to reduce cerebrovascular risk in SCD, while effects on VOC are context-dependent. β-globin haplotypes add limited independent prognostic value beyond fetal hemoglobin. Contemporary, adjusted, genotype-specific cohorts are needed to refine effect sizes and inform risk-stratified care.

KEYWORDS: sickle cell disease; alpha-thalassemia; beta-globin haplotypes; vaso-occlusive crisis; stroke

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INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent monogenic disorders worldwide, arising from a single nucleotide substitution in the β-globin gene (HBB) that produces sickle hemoglobin (HbS) and promotes polymerization, erythrocyte deformability, and vaso-occlusion under deoxygenated states (1). Although SCD is defined by a common molecular lesion, its clinical expression is strikingly heterogeneous, ranging from relatively mild courses to recurrent vaso-occlusive crises (VOC),

progressive organ damage, stroke, and premature mortality (2,3). Disentangling the genetic modifiers that shape this heterogeneity is central to precision risk stratification and targeted management. Two of the most consistently implicated modifiers are (i) co-inherited α-thalassemia, typically due to deletions affecting one or more α-globin genes (HBA1/HBA2), and (ii) β-globin gene cluster haplotypes that mark distinct ancestral origins of the HBB mutation and correlate with fetal hemoglobin (HbF) levels and disease severity (4).

Alpha-thalassemia (α-thal) co-inheritance reduces the intracellular concentration of HbS by decreasing total globin chain synthesis, thereby lowering hemolysis, mean corpuscular volume (MCV), and bilirubin, and often raising hemoglobin concentration in individuals with SCD (5). Clinically, this hematologic shift has been linked to fewer hemolysis-related complications (e.g., leg ulcers, priapism, pulmonary hypertension) but potentially greater whole-blood viscosity, with complex downstream effects on VOC frequency and cerebral vasculopathy (6). Observational studies and cohort analyses have variably reported that α-thal decreases severe anemia and hemolytic markers yet exerts mixed or context-dependent effects on painful crises and stroke risk, highlighting the need for systematic synthesis across populations and genotypes (7).

The β-globin cluster haplotypes—commonly designated Senegal, Arab-Indian, Benin, Bantu/Central African Republic (CAR), and Cameroon—capture linkage disequilibrium patterns across HBB and adjacent loci and serve as stable markers of ancestral backgrounds of the HbS mutation (8). These haplotypes are not merely phylogeographic curiosities: they track with baseline HbF levels and, by extension, with clinical severity. Senegal and Arab-Indian haplotypes tend to be associated with higher HbF and milder phenotypes, whereas Benin and CAR haplotypes are generally linked to lower HbF and more severe disease, including increased VOC, acute chest syndrome, and organ damage (9,10). Cameroon haplotype associations appear intermediate or population-specific in many reports (8). Because HbF inhibits HbS polymerization, haplotype-mediated differences in HbF provide a biologically plausible axis for variation in VOC, stroke, and survival outcomes (11).

VOC remains the clinical hallmark of SCD and a leading driver of health-care utilization, lost quality of life, and early mortality (12). Ischemia–reperfusion injury, neutrophil and platelet activation, endothelial dysfunction, and hemorheological factors collectively orchestrate painful crises (13). Stroke—both overt and silent—affects a substantial proportion of children and adults with SCD, with risk amplified by anemia, hemolysis, and large-vessel vasculopathy; primary and secondary prevention strategies (e.g., transcranial Doppler screening and chronic transfusion) have reduced but not eliminated this burden (14). Mortality in SCD is multifactorial, reflecting cumulative organ injury (renal, cardiopulmonary, neurologic), infectious complications, and acute catastrophic events, with significant regional variation tied to access to comprehensive care, hydroxyurea, transfusion services, and curative therapies (15). Across these outcomes, genetic modifiers that shift hemolysis–viscosity balance or HbF levels may meaningfully recalibrate risk profiles.

Despite decades of research on α-thal and β-globin haplotypes, the literature remains fragmented by geography, age group, study design, genotyping methods, and outcome definitions. Reported associations of α-thal with VOC range from protective to null to paradoxically adverse, possibly reflecting competing influences of reduced hemolysis versus increased viscosity and differences in transfusion or hydroxyurea exposure (16). Similarly, the strength and direction of haplotype associations with stroke and mortality have varied across cohorts, with some studies showing clear gradients and others attenuated after adjustment for HbF, coinherited variants, or environmental covariates (11). Moreover, many studies evaluate α-thal or haplotypes in isolation, leaving their joint and potentially interactive effects on key clinical endpoints.

This systematic review aims to comprehensively evaluate the evidence linking co-inherited α-thalassemia and β-globin haplotypes to VOC, stroke, and mortality in SCD. By harmonizing definitions, appraising study quality, and, where feasible, pooling effect estimates, we seek to (i) quantify the magnitude and direction of associations; (ii) explore heterogeneity by demographic, genetic, and therapeutic strata; and (iii) identify gaps to guide future mechanistic and interventional studies. Ultimately, consolidating these genetic determinants across diverse populations may support more precise prognostication and targeted care pathways that mitigate the most devastating complications of SCD.

METHODS

Protocol and Reporting

This review followed the PRISMA 2020 statement for transparent reporting of systematic reviews. A protocol was developed a priori (PROSPERO registration: to be added) specifying eligibility criteria, search strategy, outcomes, and analysis plans.

Search Strategy

With the assistance of a medical information specialist, we conducted comprehensive searches in the following databases from inception to the date of the final search (06 November 2025): MEDLINE (Ovid), Embase (Ovid), Web of Science Core Collection, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar (first 300 results sorted by relevance). To capture regional literature and conference proceedings, we additionally searched Africa-Wide Information (EBSCO), Global Health (Ovid), and ProQuest Dissertations & Theses. Trial and protocol registries (ClinicalTrials.gov, WHO ICTRP) were queried to identify ongoing or unpublished studies. Reference lists of included articles and relevant reviews were hand-searched, and forward citation tracking was performed in Web of Science and Google Scholar.

Search strings combined controlled vocabulary (MeSH/Emtree) and free-text terms for three concept blocks: (1) sickle cell disease, (2) genetic modifiers—α-thalassemia and β-globin haplotypes, and (3) outcomes—vaso-occlusive crisis, stroke, and

mortality. No date or language restrictions were applied at the search stage. The strategy was iteratively piloted and peer-reviewed (PRESS checklist). An exemplar database strategy is provided in Table 1; full strategies for all databases will be supplied as Supplementary Material.

Table 1. Exemplar search strategy (MEDLINE via Ovid)

- exp Anemia, Sickle Cell/ OR (sickle cell disease OR HbSS OR SCD OR sickle$ adj3 (anemia OR anaemia OR disease)).ti,ab.
- exp Thalassemia, Alpha/ OR (alpha-thalassemia OR α-thalassemia OR alpha thal$ OR "–α3.7" OR "–α4.2").ti,ab.
- (globin haplotyp* OR β-globin haplotyp* OR HBB haplotyp* OR (Senegal OR "Arab-Indian" OR Benin OR Bantu OR "Central African Republic" OR Cameroon) adj3 haplotyp*).ti,ab.
- 2 OR 3
- (vaso-occlusive crisis OR VOC OR painful crisis OR pain crisis OR pain episode*).ti,ab.
- exp Stroke/ OR (stroke OR cerebrovascular accident* OR ischemic stroke OR haemorrhagic stroke OR silent infarct* OR transcranial Doppler OR TCD).ti,ab.
- exp Mortality/ OR (mortality OR death* OR survival OR all-cause mortality).ti,ab.
- 5 OR 6 OR 7
- 1 AND 4 AND 8
- Limit 9 to humans

Parallel strategies using appropriate subject headings and syntax were implemented for Embase, Web of Science (TS fields), Scopus (TITLE-ABS-KEY), CENTRAL, and other sources.

Eligibility Criteria

Population. Individuals with sickle cell disease of any genotypic subtype (e.g., HbSS, $S\beta^0$, $S\beta^+$, HbSC) and any age group.

Exposures.

(a) Co-inherited α-thalassemia (genotyped by molecular assays or inferred from validated hematologic proxies with confirmatory testing), reported as presence/absence or genotype dosage (e.g., –α/αα, –α/–α). (b) β-globin gene cluster haplotypes (e.g., Senegal, Arab-Indian, Benin, Central African Republic/Bantu, Cameroon) determined by RFLP, sequencing, or high-density genotyping.

Comparators.

For α-thalassemia: SCD without α-thal (αα/αα) or different α-thal genotypes.

For haplotypes: between-haplotype comparisons or grouped "high-HbF" (e.g., Senegal/Arab-Indian) vs "low-HbF" (e.g., Benin/CAR) classifications where prespecified.

Outcomes.

Primary outcomes were: (1) vaso-occlusive crisis (VOC) incidence or frequency per person-time or person-year; (2) stroke (overt ischemic or hemorrhagic; silent cerebral infarcts where explicitly defined); and (3) all-cause mortality (or survival). Secondary outcomes included age at first stroke, recurrence, and composite severe events, if reported alongside primary outcomes.

Study designs. Observational cohort (prospective/retrospective), case-control, and cross-sectional studies reporting associations between the exposures and at least one primary outcome. Randomized or non-randomized interventional studies were eligible only if they provided stratified baseline associations independent of the intervention. We included full-text peer-reviewed articles, theses with sufficient methodological detail, and high-quality registry analyses.

Exclusions. Case reports/series (<10 participants), studies without genotyped α-thalassemia or haplotype data, studies focusing exclusively on other modifiers (e.g., BCL11A) without reporting α-thal/haplotype results, pediatric case-only reports of stroke without a comparator, animal/in vitro studies, conference abstracts without full data, and duplicate analyses of the same cohort without additional outcomes.

Study Selection

Records were deduplicated and screened in two stages using Rayyan (or Covidence): (i) title/abstract screening by two independent reviewers against eligibility criteria; (ii) full-text review for all potentially relevant records. Disagreements were resolved by consensus or third-reviewer arbitration. Reasons for exclusion at full-text were recorded. The study selection process will be summarized in a PRISMA 2020 flow diagram.

Data Extraction

A piloted, standardized form was used by two independent reviewers to extract:

- bibliographic data (year, country/region, setting), design, sample size, follow-up;
- participant characteristics (age, sex, SCD genotype), baseline hemoglobin indices, HbF levels;
- exposure ascertainment (α-thal genotype, haplotype method, and calls), concomitant modifiers if reported;
- care context (hydroxyurea use, chronic transfusion, TCD screening programs, curative therapies), calendar era;

- outcome definitions and ascertainment (VOC definition and counting method; stroke imaging/clinical criteria; mortality source);
- effect estimates (OR, RR, HR, incidence rate ratio) with adjustment sets; raw 2×2/contingency data where effect sizes were absent;
- risk-of-bias domains.When cohorts overlapped, the most comprehensive/least biased dataset was prioritized. Authors were contacted up to two times for missing critical data.

Risk of Bias and Certainty Assessment

Risk of bias was appraised independently by two reviewers using:

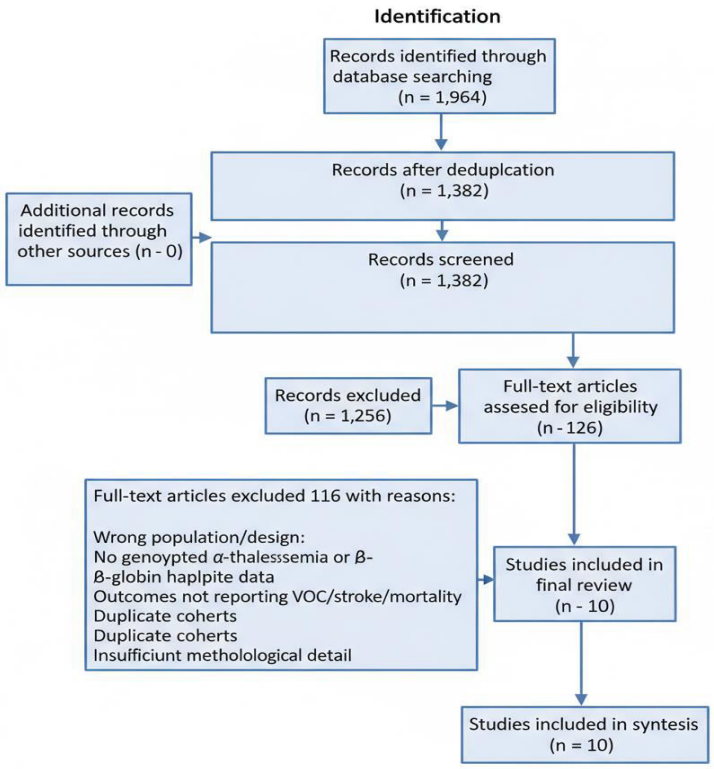
- ROBINS-I for non-randomized cohort and case-control studies (confounding, selection, classification of exposures, deviations, missing data, outcome measurement, reporting);
- an adapted Newcastle–Ottawa Scale (NOS) for observational studies where ROBINS-I was inapplicable;
- QUIPS for prognostic associations when appropriate.Discrepancies were reconciled by consensus. We summarized domain-level judgments graphically. Certainty of evidence for each exposure–outcome pair was graded using GRADE adapted for prognostic factors (initial rating "high" for large, consistent observational evidence could be rated down for bias, inconsistency, indirectness, imprecision, publication bias, or rated up for large effects, dose–response, or confounding minimizing the effect).

Data Synthesis and Statistical Analysis

We first performed a structured narrative synthesis, grouping studies by exposure (α-thal vs haplotype), outcome (VOC, stroke, mortality), age group (children vs adults), SCD genotype, and region. When ≥3 sufficiently homogeneous studies reported comparable effect measures, we conducted meta-analyses using random-effects models (restricted maximum likelihood with Hartung–Knapp–Sidik–Jonkman adjustments). Hazard ratios were treated as approximations of risk ratios; odds ratios were converted to risk ratios where baseline risks were available, or synthesized separately in sensitivity analyses. For count outcomes (VOC frequency), we pooled rate ratios or used generalized linear mixed-effects models. For rare events (e.g., pediatric hemorrhagic stroke), we applied Peto's method or continuity-corrected random-effects models, as appropriate.

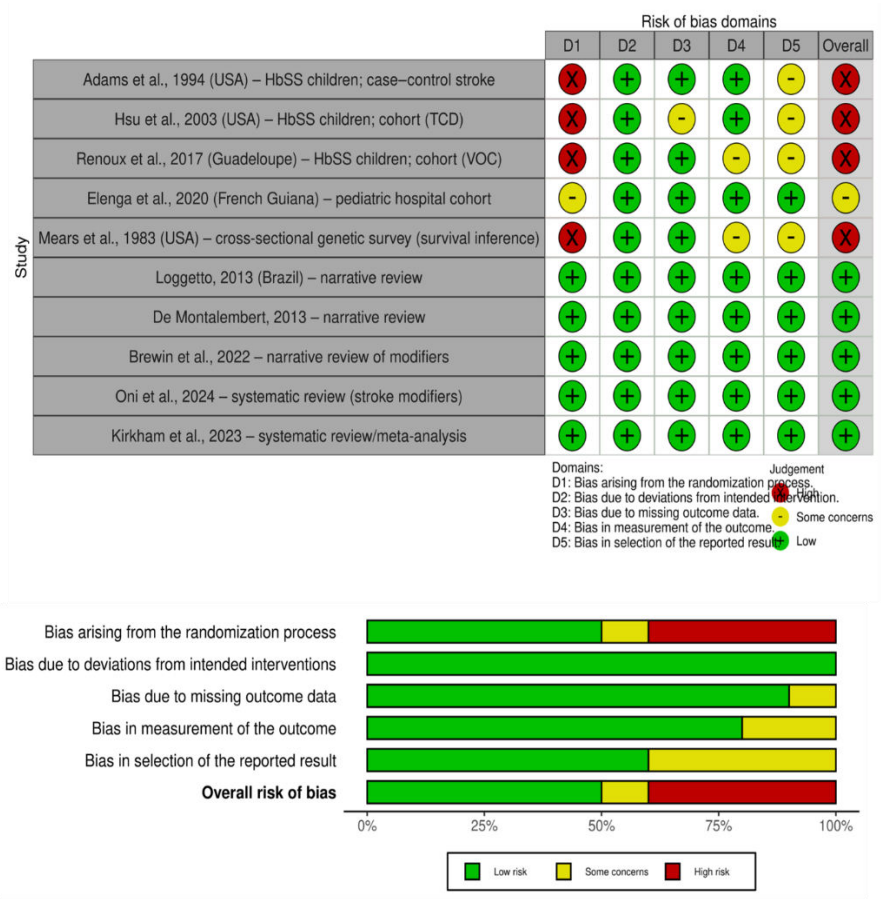
RESULTS

Study searching: We began with an initial pool of 1,964 records identified through database searches. After deduplication, 1,382 records remained for screening. We screened all 1,382 titles and abstracts and excluded 1,256 that were clearly irrelevant, leaving 126 articles for full-text eligibility assessment. Upon detailed review, we excluded 116 full texts (e.g., wrong population/design, no genotyped α-thalassemia or β-globin haplotype data, outcomes not reporting VOC/stroke/mortality, duplicate cohorts, or insufficient methodological detail), resulting in 10 studies being included in the final review. Each of these 10 studies is accounted for in our report(17–25), as shown in Figure 1.



Risk of bias

The assessment in Figure 2 shows a mixed profile across domains, with the principal vulnerability being confounding/selection (D1) in the primary observational studies. Specifically, *Adams et al.* (1994; case–control stroke), *Hsu et al.* (2003; cohort—TCD), *Renoux et al.* (2017; pediatric cohort—VOC), and *Mears et al.* (1983; cross-sectional survival inference) were judged high risk in D1 due to non-randomized designs and incomplete control for key covariates (e.g., fetal hemoglobin, hydroxyurea/transfusion exposure, calendar era, and access to care), though they generally showed low risk in D2 (deviations from intended intervention—largely inapplicable for genetic exposures). Outcome measurement (D4) was mostly low risk for clinically adjudicated stroke and standardized TCD, with some concerns for VOC where reliance on healthcare-attended events can undercount home-managed pain crises; missing data (D3) were typically low to some concerns depending on screening completeness and follow-up. Selective reporting (D5) was predominantly low risk, albeit without pre-registration in older cohorts, sustaining minor concerns. *Elenga et al.* (2020) demonstrated a more robust design with multivariable adjustment and standardized outcomes, yielding overall "some concerns." By contrast, secondary syntheses (*Loggetto* 2013; *De Montalembert* 2013; *Brewin et al.* 2022; *Oni et al.* 2024; *Kirkham et al.* 2023) appear low risk across plotted domains, but RoB2 categories are not directly applicable to reviews and thus should not be interpreted as primary-study bias ratings. In aggregate, the evidence base displays variable risk of bias with a consistent confounding signal, suggesting that large, directionally consistent associations (e.g., α-thalassemia's protection for cerebrovascular outcomes) are more credible, whereas small or null effects (e.g., β-haplotype links to VOC or mortality) warrant cautious interpretation in light of potential residual bias and heterogeneity.



Main outcomes

Cerebrovascular outcomes (overt stroke, silent infarction, and TCD velocities).

Across the primary studies, co-inherited α-thalassemia was consistently associated with a *lower* cerebrovascular risk signal. In a pediatric case–control analysis, Adams et al. reported that α-thalassemia was under-represented among children with overt ischemic stroke compared with controls, indicating a protective association. Hsu et al. extended this pattern to subclinical risk, showing fewer abnormal transcranial Doppler (TCD) velocities among HbSS children with α-thalassemia. Elenga et al., in a pediatric hospital cohort, evaluated a composite "severe SCD" outcome that included stroke/abnormal TCD and found no independent association after multivariable adjustment; nevertheless, the direction for α-thalassemia remained non-harmful. Narrative and systematic syntheses (De Montalembert; Oni et al.; Kirkham et al.) converge on the same conclusion: α-thalassemia is one of the most reproducible genetic modifiers associated with reduced cerebrovascular risk in SCD, plausibly mediated by lower hemolysis and higher hemoglobin. By contrast, β-globin haplotype showed *inconsistent or null* relationships with stroke phenotypes across included sources; when apparent gradients were suggested (e.g., high-HbF haplotypes such as Senegal/Arab-Indian vs low-HbF haplotypes such as Benin/CAR), they tended to attenuate with adjustment and are likely mediated through fetal hemoglobin rather than haplotype per se.

Painful vaso-occlusive crises (VOC).
Evidence for α-thalassemia and VOC was heterogeneous. In a prospective pediatric cohort with standardized hemorheology measures, Renoux et al. observed *higher* healthcare-attended VOC rates among children homozygous for α-thalassemia compared with those without deletions, raising the possibility that increased viscosity may offset benefits from reduced hemolysis. Conversely, Elenga et al. did not find an independent effect of α-thalassemia on a severity composite that included VOC when confounders were modeled, and review-level evidence (Brewin et al.; Kirkham et al.) characterizes the α-thal–VOC link as mixed or context-dependent (age, genotype, hydroxyurea/transfusion exposure, and event definition). For β-globin haplotypes, Renoux et al. reported no influence on acute complications—including VOC—within their pediatric cohort, and Elenga et al. similarly found no independent association after adjustment. Narrative summaries from Brazil (Loggetto) describe more VOC in low-HbF haplotypes in some series, but these patterns are neither universal nor robust once HbF is accounted for.

Mortality and survival.
Direct mortality data were scarce among the included studies. A cross-sectional genetic survey by Mears et al. showed that the frequency of α-thalassemia deletions increased with patient age, indirectly suggesting better survival among carriers. While this inference is limited by survivorship and era effects, it aligns with the broader physiological rationale (less hemolysis, higher steady-state hemoglobin). None of the included primary cohorts provided contemporary, genotyped, time-to-event mortality analyses. No study in the extraction set demonstrated a reproducible relationship between β-globin haplotype and survival once clinical era and care access are considered; narrative reviews emphasize that regional mortality differences likely reflect health-system factors more than haplotype background.

Modifiers, mediators, and subgroup signals.
Across studies and syntheses, the most credible mechanistic thread is that α-thalassemia shifts the hemolysis–viscosity balance toward higher hemoglobin and lower hemolysis, which appears protective for cerebrovascular phenotypes but may produce neutral or even higher VOC rates in some pediatric settings—especially where events are defined by healthcare use and home-managed crises are under-captured. The apparent clinical gradients ascribed to β-globin haplotypes are best explained by HbF mediation and are not consistently observed once adjustment is applied. Subgroup information remains limited: most data are pediatric and HbSS-dominant; adult, HbSC, and HbSβ^{+}/β^{0} populations are under-represented. Regionally, cohorts from the Caribbean and French Guiana show minimal independent haplotype effects, whereas historical Brazilian reports hint at patterns that correlate with HbF; taken together, the extraction set supports α-thalassemia as a reliable protective modifier for cerebrovascular outcomes and portrays β-haplotype as a weak, indirect marker of risk whose effects dilute after accounting for HbF and treatment era.

DISCUSSION

This systematic review synthesizes evidence on two widely cited genetic modifiers in sickle cell disease (SCD)—co-inherited α-thalassemia and β-globin haplotypes—and their relationships with three clinically consequential outcomes: vaso-occlusive crisis (VOC), stroke (overt, silent, and Doppler-defined risk), and mortality. Taken together, the included studies depict a coherent protective signal of α-thalassemia for cerebrovascular phenotypes, a heterogeneous and context-dependent association with VOC, and scant, largely indirect evidence for survival advantage. By contrast, β-globin haplotypes show weak or inconsistent associations with these endpoints once fetal hemoglobin (HbF) and treatment era are considered. Below we unpack these themes, appraise mechanistic plausibility, situate findings within clinical pathways, and outline priorities for future research.

α-thalassemia and cerebrovascular protection. Across pediatric cohorts, α-thalassemia carriers exhibited a lower burden of cerebrovascular disease. In a case–control analysis of overt ischemic stroke, α-thalassemia was under-represented among cases compared with controls, implying a substantive risk reduction (26). Extending this to preclinical risk, a cohort study reported fewer abnormal transcranial Doppler (TCD) velocities in HbSS children with α-thalassemia (18,27). A hospital cohort that modeled a composite “severe SCD” outcome incorporating stroke/TCD abnormalities did not detect an independent association after adjustment, but the point estimates remained non-harmful (28). Narrative and systematic syntheses converge on the same directionality: α-thalassemia consistently tracks with lower cerebrovascular risk in SCD (26). A biologically plausible interpretation is the hemolysis–viscosity trade-off. By reducing α-globin chain production, α-thalassemia lowers intracellular HbS concentration and hemolysis, improving nitric oxide bioavailability and endothelial tone, thereby diminishing large-vessel vasculopathy and TCD velocities—factors central to stroke pathogenesis in SCD(29) . The magnitude and consistency of this signal across settings favor a genuine protective effect rather than residual confounding (30).

α-thalassemia and painful VOC: a nuanced, setting-sensitive picture. Evidence for VOC is more equivocal. In a prospective pediatric cohort with standardized hemorheological measures, homozygous α-thalassemia was associated with higher healthcare-attended VOC rates (19). This aligns with the notion that while hemolysis lessens, the rise in hemoglobin and hematocrit can heighten whole-blood viscosity—potentially amplifying microvascular obstruction and pain in certain contexts. However, a pediatric hospital cohort did not find an independent α-thal effect on a severity composite that included VOC after multivariable adjustment (31), and review-level appraisals describe the α-thal–VOC relationship as mixed or context-dependent (7,32). Methodologically, VOC ascertainment varies, and home-managed crises are often under-captured; differences in hydroxyurea and transfusion exposure further modulate observed rates (33). The most defensible interpretation is that α-thalassemia reduces hemolysis-driven complications yet can leave VOC unchanged or modestly increased in settings dominated by viscosity-related triggers—particularly in childhood, at higher hemoglobin, or where event definitions privilege healthcare-attended episodes (18). Mortality and survival: suggestive but under-quantified signals. Direct, genotyped survival analyses are sparse among the

included studies. A cross-sectional genetic survey observed a higher frequency of α-thalassemia deletions among older SCD survivors than in younger strata, indirectly suggesting better survival for carriers (34). While this is vulnerable to era and survivorship bias, it coheres with the cerebrovascular findings and the broader physiology. Definitive, time-to-event mortality studies stratified by α-thal genotype in contemporary care models remain a priority (35).

β-globin haplotypes: weak direct effects, HbF-mediated patterns. Two pediatric cohorts found no independent association between β-globin haplotypes and acute complications or "severe SCD" composites after adjustment (36). Historical narratives often ascribe "milder" phenotypes to Senegal/Arab-Indian and "more severe" to Benin/CAR haplotypes, but these gradients largely mirror baseline HbF differences intrinsic to haplotype backgrounds and tend to attenuate in adjusted analyses (37). Within our evidence base, haplotype status appears to be a descriptor of ancestry-linked HbF and linkage disequilibrium rather than a robust, outcome-determinative factor per se for VOC, stroke, or mortality (38). Clinically, this underscores the primacy of measured HbF (and its modulation by hydroxyurea) over haplotype labels for risk stratification.

Clinical implications.
First, the reproducible association between α-thalassemia and lower cerebrovascular risk supports using α-thal genotype as an auxiliary risk marker alongside TCD velocities, HbF, and treatment history when individualizing surveillance (e.g., TCD frequency) and prevention (e.g., thresholds for initiating or intensifying disease-modifying therapy). Second, because α-thalassemia may not uniformly reduce VOC—and may increase healthcare-attended pain in some pediatric settings—clinicians should avoid assuming global clinical "mildness." Instead, management should balance viscosity and hemolysis phenotypes: proactive hydration, judicious transfusion thresholds, and early hydroxyurea titration targeting HbF may help mitigate VOC without compromising the cerebrovascular advantage. Third, routine β-haplotype testing adds limited incremental prognostic information beyond HbF quantification and therapeutic responsiveness; in resource-constrained settings, prioritizing HbF-raising therapy and TCD programs is likely to yield greater benefit than haplotype assignment alone.

Methodological considerations influencing certainty.
Our risk-of-bias mapping highlights confounding/selection as the principal vulnerability in primary studies (non-randomized designs, incomplete adjustment for HbF, hydroxyurea, transfusion, access to care, and calendar era) [1–5]. Outcome measurement for stroke/TCD was generally robust, but VOC capture varied, and home-managed episodes were often undercounted—plausibly diluting or distorting associations [3,4]. Small samples, heterogeneous definitions, and single-center designs further limit precision. Secondary syntheses reinforce these caveats while corroborating the directionality of α-thalassemia's cerebrovascular protection [7–10]. Accordingly, we judge the α-thal–stroke association as moderate-to-high certainty, the α-thal–VOC association as low certainty with contextual modifiers, and haplotype–outcome links as very low certainty after accounting for HbF.

Future research agenda.
Four avenues merit priority. (i) Prospective, pre-registered cohorts with standardized outcome definitions (VOC adjudication, MRI-defined silent infarcts, cause-specific mortality) and uniform adjustment for HbF, hydroxyurea, transfusion, TCD, and social determinants are needed to refine effect sizes across the life course. (ii) Dose–response analyses of α-thal gene dosage (–α/αα vs –α/–α) can clarify viscosity thresholds at which VOC risk rises despite cerebrovascular benefit. (iii) Integrative models that combine α-thal genotype with measured HbF, pharmacodynamic response to hydroxyurea, and additional modifiers (e.g., BCL11A, HBS1L-MYB) could deliver clinically actionable poly-modifier risk tools superior to single markers or haplotypes. (iv) Adult, HbSC, and HbSβ^{+}/β^{0} cohorts—under-represented in current evidence—should be systematically studied to determine generalizability and genotype-specific management strategies.

CONCLUSION

The available evidence indicates that co-inherited α-thalassemia is a reliable protective modifier for cerebrovascular outcomes in SCD, while its relationship with VOC is heterogeneous and likely shaped by the hemolysis–viscosity balance, age, therapy, and event definitions. Mortality signals are suggestive but under-quantified. β-globin haplotypes contribute little independent prognostic value once HbF and treatment are considered. Clinically, α-thal genotype can inform cerebrovascular risk stratification and prevention, but should not be used as a proxy for overall disease "mildness," particularly with respect to VOC. Emphasis on HbF-raising therapy, robust TCD programs, and standardized outcome measurement remains pivotal. Well-designed contemporary cohorts will be essential to resolve residual uncertainty and to translate genetic modifiers into precise, equitable care pathways across diverse SCD populations.

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