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Family History of Sudden Death among First-Degree Relatives of Individuals with Sickle Cell Disease or Other Hemoglobinopathies: A Narrative Review of Prevalence Evidence

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Abstract

Background: Evidence on the prevalence of a family history of sudden death in hemoglobinopathies is limited. This study synthesizes evidence concerning first-degree relatives of affected individuals and carriers and identifies gaps in understanding its clinical relevance.

***Materials and Methods*:** We searched PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, SID, Magiran, and CIVILICA for English- and Persian-language publications through June 2026. Two reviewers independently screened titles and abstracts. Evidence was classified as direct, comparative, or contextual and synthesized narratively. The primary outcome was the proportion of individuals with hemoglobinopathies or carriers with at least one first-degree relative with a history of sudden death.

Results: No extractable prevalence estimate was identified in the included literature for individuals with hemoglobinopathies or carriers. The absence of adequate numerators, denominators, and verified family-history data precluded prevalence estimation and comparisons across hemoglobinopathy types, carrier status, and categories of first-degree relatives. Studies of hemoglobinopathies primarily focused on patient mortality, arrhythmias, and cardiopulmonary complications rather than sudden death among relatives. Comparative cardiac literature reported a family history of sudden cardiac death in 34.2% of ischemic sudden-death victims, 13.4% of nonischemic victims, and 17.6% of controls without heart disease; this history was significantly more common in the ischemic group. Although these findings provide contextual information, they do not establish prevalence among individuals with hemoglobinopathies or carriers.

Conclusion: Evidence is insufficient to estimate the prevalence of a family history of sudden death among individuals with hemoglobinopathies, including carriers. Studies using standardized definitions, appropriate denominators, and validated family-history ascertainment are needed to establish prevalence and assess associations with patient outcomes. Its predictive value and screening utility remain uncertain.

Key Words: Family history, First-degree relatives, Hemoglobinopathies, Sickle cell disease, Sudden death.

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1- INTRODUCTION

Sudden death is an important clinical outcome in cardiovascular disease and several systemic disorders. It is generally described as an unexpected death; however, definitions vary according to the clinical context. Sudden cardiac death frequently involves a life-threatening ventricular arrhythmia and may occur in association with ischemic heart disease, cardiomyopathies, structural cardiac abnormalities, channelopathies, and certain cardiopulmonary disorders (1–3). Identifying individuals at risk, including through the assessment of family history, is therefore clinically important.

A family history of sudden death among first-degree relatives—parents, siblings, and children—is an important consideration in individual risk assessment. Such a history may reflect shared genetic susceptibility, inherited cardiac disorders, or the clustering of cardiovascular risk factors within families and may inform cardiac screening and family follow-up (1–3). However, its clinical relevance in individuals with chronic underlying disorders, particularly hemoglobinopathies, remains uncertain.

Hemoglobinopathies comprise inherited disorders involving structural hemoglobin variants, such as those associated with sickle cell disease, or reduced globin-chain synthesis, as in alpha- and beta-thalassemia. Sickle cell disease (SCD) is a multisystem genetic disorder characterized by chronic hemolysis, vaso-occlusion, recurrent ischemia–reperfusion injury, and progressive organ damage. These processes may contribute to pulmonary hypertension, heart failure, myocardial ischemia, arrhythmias, and pulmonary complications, placing affected individuals at risk of premature and sudden death (4–9).

Despite the literature on cardiopulmonary complications and mortality in SCD (5–9), the sources examined in this review did not provide sufficient direct, extractable data to estimate the proportion of individuals with hemoglobinopathies or carriers who had at least one first-degree relative with a history of sudden death.

Most available studies have examined mortality and cardiopulmonary complications in affected individuals or associations between family history and cardiac disease in the general population (1–3, 5–9), rather than systematically assessing sudden death among the parents, siblings, or children of affected individuals or carriers. This gap limits the evidence available to determine whether such a family history could inform risk assessment, targeted cardiac evaluation, or preventive strategies in these populations.

This narrative review aims to synthesize the available evidence on the proportion of individuals with sickle cell disease or other hemoglobinopathies, including carriers, who have at least one first-degree relative with a history of sudden death. It also contextualizes these findings using evidence from other populations, identifies gaps in the literature, and outlines priorities for studies to estimate prevalence and investigate associations with clinical characteristics and patient outcomes.

2- MATERIALS AND METHODS

2.1. Study design and review question

This study was conducted as a structured narrative review to synthesize available evidence on the prevalence of a family history of sudden death among individuals with sickle cell disease, sickle cell trait, or other hemoglobinopathies. Given the limited direct evidence, heterogeneity in definitions of sudden death, and variation in study populations and reporting methods, a narrative synthesis was considered appropriate (10).The primary review question was: “What proportion of individuals with

sickle cell disease, sickle cell trait, or other hemoglobinopathies have at least one first-degree relative with a history of sudden death?" A secondary question concerned the clinical, cardiovascular, and hematological factors associated with such a family history, where reported. Two reviewers independently screened titles and abstracts, without knowledge of each other's initial decisions. Disagreements were resolved through discussion and consensus, with consultation with a third reviewer when necessary (10, 11).

2.2. Search strategy

A structured literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, SID, Magiran, and CIVILICA. English- and Persian-language publications published through June 2026 were eligible for consideration (11).

The search strategy combined controlled vocabulary, including Medical Subject Headings (MeSH) where applicable, with free-text terms relating to "sudden death," "sudden cardiac death," "family history," "first-degree relatives," "sickle cell disease," "sickle cell trait," "hemoglobinopathies," and "thalassemia," together with their Persian equivalents. Boolean operators and truncation were used, as appropriate for each database, to combine search concepts and improve search sensitivity (11).

2.3. Inclusion and exclusion criteria

Eligible studies addressed a family history of sudden death in individuals with sickle cell disease, sickle cell trait, or other hemoglobinopathies, or provided contextual evidence on sudden death, sudden cardiac death, sudden cardiac arrest, sudden unexplained death, or cardiac mortality in these populations. Studies examining a family history of sudden death in other populations were also considered eligible as comparative evidence.

Eligible publication types included original research, including observational studies, family studies, case series, and autopsy studies, as well as systematic reviews and meta-analyses (10). Case reports were included when they provided relevant clinical information on familial patterns of cardiac arrest or sudden death.

Studies were excluded if they focused exclusively on pediatric mortality unrelated to sudden or unexpected death or provided no relevant information on the primary outcome or the prespecified comparative and contextual evidence categories (10).

2.4. Data extraction and evidence synthesis

Extracted information included the first author's name, publication year, country, study design, population characteristics, hemoglobinopathy type, disease or carrier status, outcome definition, methods of family-history ascertainment and verification, category of first-degree relative, and relevant findings. A family history of sudden death was distinguished from a family history of hemoglobinopathy and from sudden death, mortality, or arrhythmia occurring in the affected individuals themselves.

Evidence was classified into three categories according to its relevance to the review question:

- Direct evidence: studies reporting a family history of sudden death among first-degree relatives of individuals with hemoglobinopathies or carriers.
- Comparative evidence: studies reporting a family history of sudden death in other populations.
- Contextual evidence: studies examining mortality and cardiopulmonary complications in individuals with hemoglobinopathies or carriers.

Studies were examined and synthesized narratively using this framework (10). Formal risk-of-bias assessment using standardized tools was not performed. However, methodological characteristics and limitations—including participant selection, outcome definition and verification, adequacy of family-history ascertainment, and applicability to the target population—were examined descriptively (12).

The primary outcome was the proportion of individuals with hemoglobinopathies or carriers who had at least one first-degree relative with a history of sudden death, among all eligible individuals whose family history had been assessed. An extractable prevalence estimate required both a numerator—the number reporting at least one such relative—and a denominator—the total number whose family history had been assessed. Patient-level rates of mortality, sudden death, or arrhythmia were not used as substitutes for this outcome.

Findings were presented in descriptive tables according to study population, hemoglobinopathy type, and evidence category. Because sufficient direct, extractable data on the primary outcome were unavailable, no pooled prevalence estimate was calculated.

2-5. Ethical considerations

This narrative review synthesized published literature without participant recruitment, clinical interventions, biological sampling, or access to identifiable individual-level data. No new patient information was collected or identifying details reproduced. Privacy and confidentiality principles articulated in the Declaration of Helsinki informed the presentation of published information (13).

The authors sought to ensure accurate attribution, avoid plagiarism, and interpret evidence objectively and transparently (11). All potential conflicts of interest will be disclosed. Published case reports were summarized without identifying details. Consistent with the CARE guidelines' inclusion of informed consent in case reporting (14), consent procedures for the original reports remained their authors' responsibility. No additional patient consent was obtained for this review.

3- RESULTS

4-1. Characteristics and relevance of the evidence

The included evidence was heterogeneous in study populations, designs, and outcomes. Studies of hemoglobinopathies primarily examined mortality, sudden death, or cardiopulmonary complications in affected individuals. In contrast, studies specifically examining a family history of sudden death involved cardiac populations outside the target population (1, 5–9, 15).

No direct, extractable data were identified among the included sources to estimate the proportion of individuals with hemoglobinopathies or carriers who had at least one first-degree relative with a history of sudden death. The evidence therefore consisted of comparative studies of family history in other populations and contextual studies of hemoglobinopathy-related outcomes. **Table 1** summarizes the characteristics of the included studies and their relevance to the review question.

A family history of hemoglobinopathy was distinguished from a family history of sudden death. The presence of sickle cell disease in relatives, without documentation of sudden death, was insufficient to establish a positive family history of the outcome of interest (16). Similarly, mortality, arrhythmias, and cardiac complications in affected individuals were not treated as substitutes for family-history data (17–19).

Table-1: Characteristics of included studies and their relevance to estimating the prevalence of a family history of sudden death.

Authors, (Reference)	Design and population	Principal outcome or information	Relevant family-history information	Contribution to the review
Kaikkonen et al. (1)	Case–control study involving acute coronary events	Association between family history and sudden cardiac death	Sudden cardiac death among first-degree relatives was assessed.	Comparative evidence from a population not specifically selected for hemoglobinopathies
Manci et al. (6)	Autopsy study of individuals with sickle cell disease	Causes of death, including sudden or unexpected death	No specific prevalence estimate for a family history of sudden death was reported.	Contextual evidence on mortality in affected individuals
Hookana et al. (15)	Comparative study of victims of ischemic and nonischemic sudden cardiac death and controls	Frequency of a family history of sudden cardiac death	Sudden cardiac death among first-degree relatives was verified using death certificates.	Quantitative comparative evidence from outside the target population
Niraimathi et al. (16)	Report of three sudden deaths in individuals with sickle cell anemia	Clinical and pathological characteristics of the deceased patients	A family history of sickle cell disease, rather than sudden death, was reported in two cases.	Illustrates the distinction between familial disease and a family history of sudden death
d'Humières et al. (17)	Prospective study of 100 individuals with sickle cell anemia	Ventricular arrhythmias assessed using 24-hour Holter monitoring	No specific prevalence estimate for a family history of sudden death was reported.	Contextual evidence on cardiac outcomes in affected individuals
Nelson et al. (18)	Observational study of 47,944 Black U.S. Army soldiers	Mortality and rhabdomyolysis in relation to sickle cell trait	Sudden death among relatives was not a study outcome.	Contextual evidence on outcomes associated with carrier status
Kirk et al. (19)	Multicenter study of 652 individuals with thalassemia major	Heart failure and arrhythmias in relation to cardiac T2*	No specific prevalence estimate for a family history of sudden death was reported.	Contextual evidence on cardiac complications in thalassemia
Weeks et al. (20)	Systematic review concerning sickle cell trait	Evidence concerning the attribution of sickle cell crises and exertion-related death to carrier status	No specific prevalence estimate for a family history of sudden death was reported.	Contextual evidence for interpreting outcomes associated with carrier status

Note: This table describes the relevance of studies to the review question and does not constitute a formal risk-of-bias assessment. The absence of a reported prevalence estimate does not necessarily indicate that family-history information was not collected.

4-2. Direct evidence on prevalence in the target population

No direct, extractable estimate was identified for the proportion of individuals with hemoglobinopathies or carriers who had at least one first-degree relative with a history of sudden death. The relevant studies did not report the required numerator and denominator, together with sufficient information on outcome definition and ascertainment, in a form that permitted calculation of the primary outcome (5–9,16,17–20).

Data were also insufficient to estimate this proportion separately according to whether the relative was a parent, sibling, or offspring. Consequently, neither an overall prevalence estimate nor comparisons between affected individuals and carriers or across hemoglobinopathy subgroups could be calculated. **Table 2** summarizes the availability of estimates in the target population and presents the comparative estimates.

4-3. Comparative evidence on a family history of sudden death

Hookana et al. studied 596 victims of ischemic sudden cardiac death, 223 victims of nonischemic sudden cardiac death, and 475 controls without heart disease. A history of sudden cardiac death in at least one first-degree relative was reported in 34.2% of the ischemic group, 13.4% of the nonischemic group, and 17.6% of controls. A positive family history was significantly more frequent in the ischemic group than in either of the other groups. The difference between the nonischemic group and controls was not statistically significant (15).

Kaikkonen et al. also reported an association between a family history of sudden cardiac death and an increased risk of sudden death during an acute coronary event (1). These findings concern cardiac populations and do not provide prevalence estimates for individuals with hemoglobinopathies or carriers.

The percentages reported by Hookana et al. apply to the populations examined in that study. They were not interpreted as estimates for individuals with hemoglobinopathies, carriers, or the general population (15).

Table-2: Availability of estimates for the proportion of individuals with at least one first-degree relative with a history of sudden death in the target and comparative populations.

Evidence category	Population	Available estimate or data status	Interpretation
Target population	Individuals with sickle cell disease	No direct, extractable estimate was identified.	Prevalence could not be calculated; patient-level outcomes were not substituted for the family-history outcome.
Target population	Individuals with sickle cell trait	No direct, extractable estimate was identified.	Prevalence could not be estimated or compared with that in affected individuals.
Target population	Individuals with other hemoglobinopathies or carriers	Data were insufficient for subgroup-specific estimates.	Comparisons across hemoglobinopathy types and between disease and carrier states

Evidence category	Population	Available estimate or data status	Interpretation
			were not possible.
Comparative evidence	Victims of ischemic sudden cardiac death	34.2% had at least one first-degree relative with a history of sudden cardiac death (15).	Estimate from a cardiac population, not a hemoglobinopathy population
Comparative evidence	Victims of nonischemic sudden cardiac death	13.4% had at least one first-degree relative with a history of sudden cardiac death (15).	The difference from controls was not statistically significant.
Comparative evidence	Controls without heart disease in the Hookana study	17.6% had at least one first-degree relative with a history of sudden cardiac death (15).	Estimate from the study control group, not a general-population prevalence estimate

Note: The primary review outcome concerned a history of sudden death in at least one first-degree relative. The comparative estimates specifically concerned sudden cardiac death. The denominator was the number of individuals assessed, not the number of relatives.

4-4. Contextual evidence by haemoglobinopathy status

4-4-1. Sickle cell disease

Mortality and autopsy studies described sudden or unexpected death in individuals with sickle cell disease. Clinical reviews also reported cardiopulmonary complications, including pulmonary hypertension, cardiac dysfunction, and arrhythmias (5–9). These findings concerned outcomes in affected individuals and did not provide sufficient information to estimate the prevalence of a family history of sudden death.

Niraimathi et al. reported three individuals with sickle cell anemia who died within the first three days of hospitalization. Relatives reported a family history of sickle cell disease after death in two cases; however, this information did not establish a history of sudden death among first-degree relatives (15).

In the study by d'Humières et al., the study-defined ventricular-arrhythmia outcome occurred in 22 of 100 patients. This proportion concerned arrhythmias in patients referred for cardiac evaluation, not sudden death or a family history of sudden death (17).

4-4-2. Sickle cell trait

Nelson et al. found no statistically significant difference in mortality between individuals with and without sickle cell trait (hazard ratio, 0.99; 95% confidence interval, 0.46–2.13). However, sickle cell trait was associated with an increased risk of exertional rhabdomyolysis (adjusted hazard ratio, 1.54; 95% confidence interval, 1.12–2.12). Sudden death among first-degree relatives was not a study outcome (18). The systematic review by Weeks et al. found no evidence supporting the attribution of exertion-related death to sickle cell trait alone in the absence of rhabdomyolysis. The review addressed the attribution of death in carriers and did not estimate the prevalence of a family history of sudden death (20).

4-4-3. Thalassaemia and other haemoglobinopathies

Kirk et al. reported an association between myocardial iron overload and heart failure or arrhythmias in individuals with thalassemia major. These outcomes were measured in affected individuals; the prevalence of a family history of sudden death was not estimated (19).

Among the included sources, direct data were insufficient to estimate prevalence in other hemoglobinopathy subgroups or to compare affected individuals with carriers. Findings concerning cardiac complications in thalassemia major were therefore not extrapolated to other hemoglobinopathies or carrier states.

4-5. Sufficiency of evidence for prevalence estimation and subgroup comparisons

The principal reporting gaps were the absence of appropriate numerators and denominators, insufficient information to distinguish family-history outcomes by category of first-degree relative, and limited information on relatives' ages and verified causes of death. Data were also insufficient for comparisons between affected individuals and carriers or across hemoglobinopathy subgroups.

Overall, the included evidence did not support estimation of the primary outcome or subgroup comparisons. This finding reflects the absence of sufficient direct, extractable data in the sources examined; it does not establish that no relevant studies exist in the wider literature.

4- DISCUSSION

This narrative review examined the available evidence on the prevalence of a family history of sudden death among individuals with sickle cell disease or other hemoglobinopathies, including carriers, and contextualized the findings using evidence from other populations. The principal finding was that the included literature did not provide sufficient direct, extractable data to estimate this prevalence or compare it across hemoglobinopathy types and disease or carrier states. Studies of hemoglobinopathies primarily examined mortality, arrhythmias, and cardiopulmonary complications in affected individuals, whereas studies specifically addressing a family history of sudden death involved cardiac populations (1, 5–9, 15–20). Interpreting this evidence therefore requires distinguishing its clinical relevance from its ability to answer the specific review question.

5-1. Interpretation of the Principal Finding and the Evidence Gap

The absence of an extractable prevalence estimate should not be interpreted as evidence that a family history of sudden death is uncommon or clinically unimportant in the target population. Rather, it indicates that the information reported in the included studies was insufficient to measure the outcome of interest. Estimating this prevalence requires both the number of affected individuals or carriers with at least one first-degree relative with a history of sudden death and the total number whose family history was assessed. Reports of sudden death or arrhythmias in patients themselves cannot provide this estimate.

Autopsy studies and investigations of mortality in sickle cell disease help characterize fatal complications and underlying conditions. However, their primary focus is death in the affected individual, rather than a family history of sudden death (6, 7, 15). Similarly, studies of cardiovascular abnormalities and ventricular arrhythmias describe patients' clinical characteristics but do not establish familial clustering of sudden death (5, 9, 17).

The identified gap therefore reflects a mismatch between the review question and

the information reported in the included literature. Patient-level outcomes and family-history indicators may both concern sudden death, but their numerators, denominators, and interpretations differ. An important contribution of this review is to make this distinction explicit and avoid treating patient-level outcomes as substitutes for family-history data. Nevertheless, this finding is limited to the sources examined and does not establish that no relevant studies exist elsewhere in the literature.

5-2. Comparison with Evidence from Other Populations

Evidence from cardiac populations suggests that a family history of sudden cardiac death can be associated with individual risk. Kaikkonen et al. reported an association between family history and sudden cardiac death during an acute coronary event. Hookana et al. reported differences in the frequency of a positive family history among victims of ischemic sudden cardiac death, victims of nonischemic sudden cardiac death, and controls (1, 16). These findings highlight the importance of the underlying disease context: a family-history indicator may not have the same clinical meaning or strength of association across populations.

The prospective study by Bagnall et al. further illustrated the contribution of genetic investigation to understanding unexplained sudden cardiac death. A clinically relevant cardiac genetic finding was identified in 31 of 113 genetically tested cases, corresponding to 27% of those tested (21). This percentage represents the diagnostic yield of genetic testing in a selected subgroup of sudden-death victims, not the prevalence of a family history of sudden death among individuals with hemoglobinopathies.

Differences in population selection limit quantitative comparisons. Studies recruiting sudden-death victims and their families begin with an index death. In contrast, a study addressing the primary question of this review would recruit individuals with a hemoglobinopathy or carrier status and ascertain whether sudden death had occurred in their first-degree relatives. Findings from other populations may therefore inform hypotheses and approaches to familial evaluation, but their percentages cannot be transferred directly to the target population.

The comparison in this review is consequently interpretive rather than quantitative. Cardiac studies suggest that family history may be relevant in particular settings, whereas the included hemoglobinopathy literature remains insufficient to establish its frequency or clinical significance. This contrast supports population-specific research but does not itself demonstrate increased familial risk.

5-3. Distinguishing Individual Outcomes, Family History, and Cause of Death

Three concepts must remain separate: sudden death in the affected individual, a history of sudden death in a first-degree relative, and the underlying cause of that relative’s death. Information about one does not necessarily establish the others. For example, ventricular arrhythmias in patients with sickle cell anemia provide information about their cardiac status but do not demonstrate familial clustering of sudden death (17). Likewise, a family history of sickle cell disease, without documentation of sudden death in relatives, does not establish a positive history for the primary outcome (15).

Even when sudden death is reported in a first-degree relative, attributing that death to a hemoglobinopathy requires additional evidence. The deceased relative’s disease or carrier status may be unknown, and the presence of a hemoglobinopathy in the family does not establish the cause of

death. The APHRS/HRS consensus statement and related reviews describe the investigation of unexplained sudden death as integrating clinical information, circumstances of death, autopsy findings, and, where appropriate, genetic testing and evaluation of relatives (3, 22).

Future studies should therefore record outcome verification and cause-of-death classification separately. Family-reported sudden death, documented sudden death, and confirmed sudden cardiac death should not be treated as equivalent. Furthermore, confirmation that a death was sudden does not necessarily establish its underlying cause. Maintaining these distinctions would reduce the risk of treating an uncertain family report as both a confirmed outcome and evidence of a hemoglobinopathy-related death.

5-4. Heterogeneity of Hemoglobinopathies and the Need for Subgroup Analysis

Sickle cell disease, sickle cell trait, and thalassemia should not be treated as clinically interchangeable. Cardiopulmonary complications and arrhythmias have been investigated in sickle cell disease, whereas myocardial iron overload is associated with cardiac complications in thalassemia major (5, 9, 17, 19). These differences suggest that a single estimate combining all hemoglobinopathies could obscure clinically relevant subgroup variation.

A systematic review found that the strength of evidence for clinical outcomes associated with sickle cell trait varied by outcome. High-strength evidence supported associations with pulmonary embolism, proteinuria, and chronic kidney disease, whereas moderate-strength evidence supported an association with exertional rhabdomyolysis. Evidence for many other outcomes was insufficient or of low strength (23). Together with observational findings and a review of exertion-related death, these results reinforce the need to avoid extrapolating risks associated with sickle cell disease to carriers or automatically attributing exertion-related deaths to carrier status (18, 20, 23). For transfusion-dependent thalassemia, clinical guidelines emphasize monitoring iron overload and assessing cardiac complications (24). Although these factors are important for patient management, they do not establish the prevalence of a family history of sudden death. Future studies should therefore record the hemoglobinopathy type, genotype, and disease or carrier status of the index individual and, where possible, the deceased relative.

Accurate diagnostic classification is also relevant to the design of future family-history studies. A discussion of empirical iron prescribing in children with anemia highlights the limitations of treatment without appropriate diagnostic evaluation in populations with a high prevalence of thalassemia (25). Although this publication does not address familial sudden death, it illustrates the importance of establishing the underlying hematological diagnosis. For the present research question, disease and carrier classifications should likewise be documented rather than inferred from anemia alone.

5-5. Associations with Clinical Findings and Patient Outcomes

A secondary objective of this review was to examine reported associations between a family history of sudden death and clinical findings or patient outcomes. The included evidence was insufficient to establish such a history as a predictor of arrhythmias, cardiac dysfunction, or mortality in individuals with hemoglobinopathies. Demonstrating that these outcomes occur in affected individuals does not establish an association with family history unless that relationship is directly examined.

Potential relevance must therefore be distinguished from demonstrated predictive value and clinical utility. Even if future studies identify a substantial prevalence of positive family history, frequency alone would not establish its ability to predict subsequent outcomes. This would require evidence that family history adds prognostic information beyond relevant patient characteristics. Clinical utility would require further evaluation of whether using that information improves clinical decisions or outcomes.

This review provides no evidentiary basis for recommending routine cardiac or genetic screening of all first-degree relatives solely because an individual has a hemoglobinopathy. Conversely, the absence of direct prevalence data should not be interpreted as evidence against evaluation when unexplained sudden death has occurred in a family. Such a death should not be attributed to a hemoglobinopathy solely because the condition is present; evaluation should consider the circumstances of death and the possibility of an inherited cardiac disorder, consistent with established approaches to unexplained sudden death (3, 22). Collecting family-history information and deciding whether specialist investigation is indicated are distinct activities.

Communication with families is a further consideration when discussing uncertainty and the possible need for evaluation. In pediatric oncology, longitudinal, competency-based training in empathy and breaking bad news has been proposed, with an emphasis on observed communication performance, developmentally appropriate language, and family understanding (26). Although this educational proposal does not establish clinical benefit in hemoglobinopathies, it offers a framework that could be adapted and evaluated for communicating the distinction between a reported family history, a verified event, and an established inherited risk. Such communication should make uncertainty explicit without presenting a positive family history as a confirmed predictor of patient outcomes.

5-6. Research Priorities

The first priority is to conduct studies that directly measure the primary outcome. These studies should report the number of individuals with at least one first-degree relative with a history of sudden death and the total number whose family history was assessed. The number of individuals with a positive family history must be distinguished from the number of relatives who died suddenly. Unknown or incomplete family-history status should be reported separately rather than classified as negative.

Valid comparisons require consistent or comparable definitions of sudden death, ascertainment methods, and verification procedures. Studies should also record the age of the index individual, the number and ages of first-degree relatives, and relevant family structure. These characteristics affect the opportunity for a death to have occurred and been reported. Where available, medical records, death certificates, and autopsy reports may help distinguish family-reported events from documented outcomes.

Prevalence studies should be complemented by longitudinal investigations examining associations between family history and subsequent patient outcomes. Analyses should distinguish disease from carrier status, evaluate hemoglobinopathy subgroups separately, and account for relevant demographic and clinical factors. Measuring prevalence, evaluating associations, and assessing clinical utility are related but distinct research tasks; none should be treated as sufficient, on its own, to justify a screening recommendation.

The feasibility of longitudinal research also depends on maintaining follow-up when access to care is disrupted. Rostami et al. described adaptations in an Iranian pediatric hematopoietic stem cell transplantation service during the COVID-19 pandemic, including telephone follow-up, teleconsultation, and virtual support for patients and families (27). This report did not investigate familial sudden death, but it provides a service-level example of approaches to maintaining contact under constrained conditions. Future hemoglobinopathy cohorts could evaluate whether comparable approaches improve follow-up completeness, while ensuring that remote family reports are distinguished from independently verified death information.

5-7. Strengths and Limitations

A strength of this review was its focus on a clearly defined family-history outcome and its distinction from mortality and cardiac complications in affected individuals. Separating direct, comparative, and contextual evidence also prevented estimates from cardiac populations from being interpreted as prevalence estimates for the target population.

Nevertheless, the narrative design and restriction to English- and Persian-language publications leave open the possibility that relevant sources were missed. Heterogeneity in populations, outcomes, and reporting methods further limited comparability. No formal risk-of-bias assessment was undertaken; the descriptive examination of methodological limitations should therefore not be interpreted as a standardized assessment of evidence quality or certainty.

The findings also depended on published reporting. Failure to report family history does not necessarily mean that it was not collected. Accordingly, the principal inference concerns the adequacy of the included literature for answering the review question. It does not establish the complete absence of relevant studies, a low underlying prevalence, or the absence of associations with clinical outcomes.

5- CONCLUSION

The included literature did not provide sufficient direct, extractable data to estimate the proportion of individuals with hemoglobinopathies or carriers who had at least one first-degree relative with a history of sudden death, or to compare this proportion across subgroups. Evidence on patient-level outcomes and family history in cardiac populations provides context but cannot substitute for a population-specific estimate. Future studies should use standardized outcome definitions, appropriate denominators, clearly documented family-history ascertainment and verification, and separate analyses of disease and carrier states. Such studies are needed to establish prevalence and evaluate associations with clinical findings and subsequent patient outcomes. The predictive value of this family history and the clinical utility of screening based on it remain uncertain in the target population.

6- CONFLICT OF INTEREST: None.

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