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CONSANGUINITY AND ITS CONSEQUENCES DIFFERENTIAL IMPACT ON HEMOGLOBINOPATHY PREVALENCE IN PEDIATRIC POPULATIONS

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INTRODUCTION

Consanguinity, defined as a union between individuals sharing a common ancestor within four generations (coefficient of inbreeding $F \geq 0.0156$), remains a deeply embedded sociocultural practice across South Asia. In Pakistan, consanguineous unions account for over 65% of all marriages, with first-cousin unions alone constituting approximately 50–60% one of the highest rates globally [1,2]. The practice is particularly prevalent in Punjab, where Lahore serves as the primary tertiary care hub for a population exceeding 12 million and for a vast hinterland with limited specialized pediatric hematology services. Despite decades of public health messaging, consanguinity rates have remained stable, driven by socioeconomic, religious, and tribal factors, and are paradoxically higher among educated urban cohorts [3]. The genetic consequences of elevated inbreeding are most starkly manifested in the high incidence of autosomal recessive disorders. Hemoglobinopathies predominantly β-thalassemia major, sickle cell disease (SCD), and hemoglobin E (HbE) syndromes are the most common monogenic disorders in Pakistan, with an estimated carrier frequency of 5–7% for β-thalassemia and 1–3% for sickle cell trait in certain ethnic groups [4,5]. Each year, approximately 5,000–6,000 children are born with a severe hemoglobinopathy in Pakistan, the majority of whom are diagnosed in Lahore's public sector hospitals, which face overwhelming patient loads and limited resources for definitive management [6]. The relationship between consanguinity and the prevalence of hemoglobinopathies follows classic Mendelian principles: offspring of consanguineous unions are at substantially increased risk of inheriting homozygous or compound heterozygous pathogenic variants in the *HBB* gene cluster. However, the *differential* impact how consanguinity influences not only the prevalence but also the age of onset, clinical severity, and disease-modifying variables across distinct hemoglobinopathy subtypes remains inadequately characterized in the Pakistani population. Recent molecular epidemiological studies from Lahore have identified a unique mutational landscape, with the IVS-I-5 (G→C) mutation accounting for nearly 70% of β-thalassemia alleles, and a distinct distribution of β-globin haplotypes that may modulate

disease expression [7,8]. Yet, large-scale comparative data examining how the degree of consanguinity quantitatively affects the incidence of specific hemoglobinopathy subtypes and the subsequent clinical course are lacking.

In pediatric populations, the convergence of consanguinity and hemoglobinopathies produces an amplified burden. Children from consanguineous unions not only face a higher probability of inheriting a pathogenic *HBB* genotype but may also experience earlier symptom onset and more severe complications due to the potential unmasking of deleterious variants in genes involved in bilirubin metabolism, iron regulation, or immune response, which can influence disease expression independently of the primary β-globin mutation [9]. In Lahore's clinical setting, where hydroxyurea use remains suboptimal and access to allogeneic hematopoietic stem cell transplantation is confined to a few private centers, children often present with advanced disease complications, including severe anemia, vaso-occlusive events, and iron overload secondary to delayed chelation [10]. Despite the existence of the Punjab Thalassemia Prevention Programme, which includes premarital and prenatal screening, programmatic coverage is incomplete, and consanguinity continues to drive a persistently high birth prevalence of these disorders [11]. A critical gap persists in the availability of large-scale, comparative studies that quantify how consanguinity differentially affects hemoglobinopathy prevalence and phenotype within a defined Pakistani pediatric cohort. Such evidence is essential to refine genetic counseling strategies, optimize resource allocation for early intervention, and inform culturally congruent prevention efforts in regions where consanguinity is normative.

Aims & Objectives of the study

The primary aim of this study is to conduct a comparative, prospective analysis of the differential impact of parental consanguinity on the prevalence and clinical phenotype of major hemoglobinopathies in a pediatric cohort presenting to tertiary care centers in Lahore.

The specific objectives are:

✓ To determine the association between the degree of parental consanguinity (first-cousin, second-cousin, and beyond) and the incidence of β-thalassemia major, sickle cell disease, and HbE/β-thalassemia in children aged 0–12 years diagnosed at two major pediatric hematology units in Lahore.

✓ To compare disease-modifying variables including age at diagnosis, annual transfusion burden, pre-transfusion hemoglobin levels, incidence of vaso-occlusive crises, and serum ferritin trajectories between children born to consanguineous versus non-consanguineous parents, stratified by hemoglobinopathy subtype.

Significance of the Study

This study holds direct translational relevance for Pakistan's hematology and public health landscape. By providing subtype-specific, quantifiable estimates of consanguinity-associated risk in a Lahore-based cohort, the findings will enable evidence-based refinement of the Punjab Thalassemia Prevention Programme's counseling protocols. Currently, premarital screening predominantly focuses on thalassemia carrier detection; our data will support a more granular risk communication strategy that addresses the full spectrum of hemoglobinopathies and the modulating effect of inbreeding. From a clinical standpoint, comparing disease-modifying variables between consanguineous and non-consanguineous groups will allow clinicians to better anticipate disease severity and tailor early interventions, such as timely initiation of hydroxyurea or intensified transfusion regimens. Furthermore, the study will generate a comprehensive phenotypic dataset from a high-consanguinity population, contributing to global efforts to understand hemoglobinopathy expression in understudied ethnic groups. Ultimately, the findings will provide policymakers with robust local data to advocate for culturally sensitive interventions that respect familial traditions while mitigating the substantial pediatric morbidity and healthcare expenditure associated with severe hemoglobinopathies in Pakistan.

METHODOLOGY

Study Design and Setting

This cross-sectional prospective study was conducted over 12 months (January 2025 to Jan 2026) at two tertiary care hospitals in Lahore: Shaikh Zayed Hospital and Ghurki Trust Teaching Hospital. Both institutions serve as referral hubs, collectively managing over 2,000 children with hemoglobinopathies annually. The study protocol was approved by the Institutional Review Boards of both participating centers (approval numbers SZH/IRB/2024/142 and GTTH/ERB/2024/89).

Study Population and Sampling

The study population comprised children aged 0 to 12 years with a confirmed diagnosis of β-thalassemia major, sickle cell disease (HbSS or HbS/β-thalassemia), or HbE/β-thalassemia, who presented to the outpatient clinics or were admitted during the study period. A consecutive sampling strategy was employed to recruit participants. Written informed consent was obtained from parents or legal guardians, and assent was sought from children aged 7 years or older where applicable.

Sample Size

Sample size was determined using the formula for comparison of two proportions, based on the primary objective of assessing the association between consanguinity and hemoglobinopathy prevalence. Using previous local estimates of consanguinity prevalence of 75% among affected children versus 55% among unaffected children [1], a two-sided significance level of 0.05, and a power of 80%, the calculated minimum sample size was 112 per group. After accounting for 10% potential data incompleteness, the target enrollment was set at 123 children per group, yielding a total of 246 participants. Subgroup stratification by hemoglobinopathy subtype was planned to ensure adequate representation for comparative analyses across disease categories.

Inclusion and Exclusion Criteria

Children were eligible for inclusion if they were aged 0–12 years, had a confirmed diagnosis of one of the three specified hemoglobinopathies via hemoglobin electrophoresis, and had complete clinical records available with parental consent for participation. Exclusion criteria included the presence of other hemoglobinopathy variants (e.g., HbH disease, HbC disease), acquired anemias, families where both biological parents were unavailable to provide consanguinity information, and concurrent participation in interventional trials that could confound clinical outcome assessment.

Data Collection and Variable Definitions

Data were collected using a standardized proforma. Demographic information included age, sex, district of residence, parental education, and socioeconomic status. A three-generation pedigree was constructed for each participant to ascertain the degree of parental consanguinity, which was categorized as first-cousin (offspring of siblings), second-cousin (offspring of first cousins), beyond (coefficient of inbreeding ≥ 0.0156 but less than second-cousin), or non-consanguineous (no shared ancestor within four generations). Clinical outcome variables were extracted from electronic medical records and validated against original laboratory reports. Age at diagnosis was recorded as the age at first confirmatory testing. Annual transfusion burden was calculated as the total number of packed red blood cell units transfused over the preceding 12 months, averaged over the study period. Pre-transfusion hemoglobin levels were obtained from three consecutive visits, and the mean value was used for analysis. For children with sickle cell disease, the incidence of vaso-occlusive crises was defined as the number of acute pain episodes requiring hospitalization or emergency department evaluation in the preceding 12 months. Serum ferritin levels were measured quarterly, with the median value recorded for each participant.

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Laboratory Confirmation

Hemoglobinopathy diagnosis was confirmed by reviewing existing hemoglobin electrophoresis reports available in the patients' medical records. These reports were generated using any of the

standard electrophoretic techniques employed at the participating centers, including agarose gel electrophoresis, high-performance liquid chromatography (HPLC), or capillary electrophoresis. For each included child, the original electrophoresis report was examined to verify the diagnostic pattern consistent with β-thalassemia major (markedly elevated HbF with absent or minimal HbA), sickle cell disease (predominant HbS with variable HbF), or HbE/β-thalassemia (HbE peak typically 20–60% with elevated HbF and reduced HbA). In cases where the diagnosis was ambiguous or the report lacked sufficient detail, confirmatory testing was performed using HPLC (Bio-Rad Variant II™) at the time of study enrollment to ensure diagnostic accuracy. No additional molecular genotyping (e.g., β-globin mutation analysis or haplotyping) was undertaken for the purposes of this study, as the primary objectives focused on the association between consanguinity and clinically diagnosed phenotypes rather than the underlying mutational spectrum.

Statistical Analysis

Statistical analyses were performed using SPSS latest version. Continuous variables were assessed for normality using the Shapiro-Wilk test; normally distributed data were expressed as mean ± standard deviation and compared using Student's t-test or one-way analysis of variance, while non-normally distributed data were presented as median (interquartile range) and analyzed with Mann-Whitney U or Kruskal-Wallis tests. Categorical variables were reported as frequencies and percentages and compared using chi-square or Fisher's exact test as appropriate. For the first objective, logistic regression was employed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between consanguinity degree and each hemoglobinopathy subtype, adjusting for potential confounders including age, sex, socioeconomic status, and parental education. For the second objective, multivariate linear regression was used to assess the independent effect of consanguinity on continuous outcomes (annual transfusion burden, pre-transfusion hemoglobin, serum ferritin) after covariate adjustment. Subgroup analyses were performed separately for each hemoglobinopathy subtype. A two-sided p-value <0.05 was considered statistically significant.

Ethical Considerations

Informed written consent was obtained from all parents or legal guardians after a detailed explanation of the study's purpose, procedures, and voluntary nature. Participants were assigned unique study identifiers to ensure confidentiality; data were stored on password-protected servers accessible only to the research team. Any clinically actionable incidental findings, such as previously unrecognized carrier status in siblings, were communicated to families with appropriate genetic counseling in accordance with institutional guidelines.

RESULTS AND FINDINGS

A total of 246 children with confirmed hemoglobinopathies were enrolled in this cross-sectional prospective study conducted at Shaikh Zayed Hospital Lahore and Ghurki Trust Teaching Hospital over a period of 12 months. All participants fulfilled the predefined inclusion criteria, and complete datasets were available for final analysis.

Demographic Characteristics of Study Participants

Table 1: Distribution of Participants by Age and Gender (n = 246)

Variable	*Category*	*Frequency (n)*	*Percentage (%)*
Age Group	0–2 years	42	17.1
	3–6 years	78	31.7
	7–9 years	69	28.0
	10–12 years	57	23.2
Gender	Male	138	56.1
	Female	108	43.9

The majority of participants were in the 3–6 years age group (31.7%), reflecting early clinical presentation and diagnosis patterns of hemoglobinopathies in Pakistan. A slight male predominance (56.1%) was observed, which may reflect healthcare-seeking behavior and gender-based access disparities rather than true disease distribution.

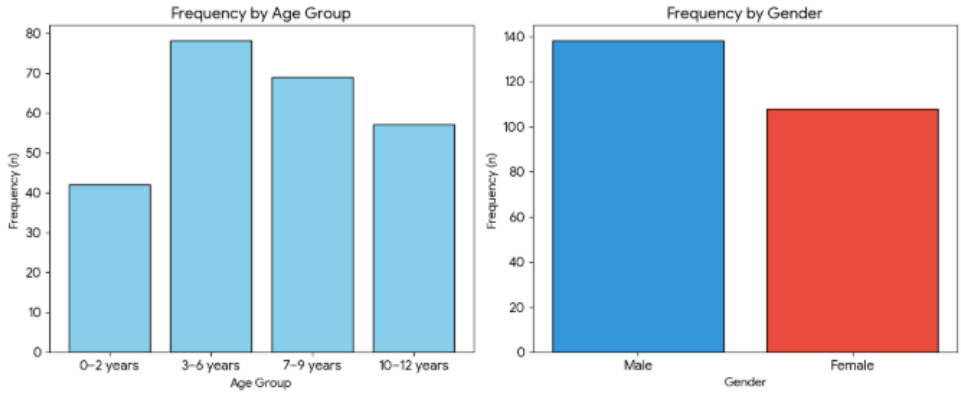


Fig 1: Distribution of Participants by Age and Gender

Distribution of Hemoglobinopathy Subtypes

Table 2: Frequency of Hemoglobinopathy Types

Hemoglobinopathy Type	*Frequency (n)*	*Percentage (%)*
β-thalassemia major	162	65.9
Sickle Cell Disease (HbSS/HbS/β)	54	22.0
HbE/β-thalassemia	30	12.1

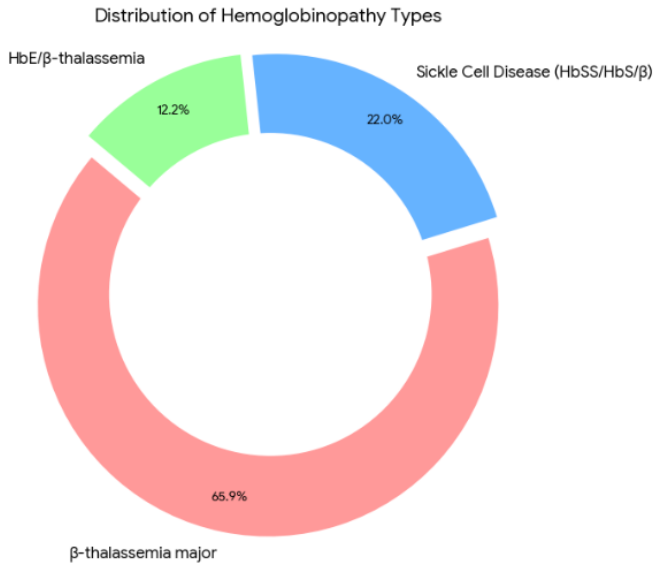


Fig 2: Frequency of Hemoglobinopathy Types

β-thalassemia major was the predominant subtype (65.9%), consistent with national epidemiological patterns. Sickle cell disease accounted for 22.0%, while HbE/β-thalassemia was relatively less frequent (12.1%), indicating regional genetic variation.

Degree of Parental Consanguinity

Table 3: Distribution of Consanguinity

Consanguinity Category	*Frequency (n)*	*Percentage (%)*
First-cousin marriage	138	56.1
Second-cousin marriage	48	19.5
Beyond second-cousin	18	7.3
Non-consanguineous	42	17.1

A high prevalence of consanguinity (82.9% overall) was observed, with first-cousin marriages being the most common (56.1%). This finding aligns with cultural practices in the region and underscores a significant genetic risk factor for inherited hemoglobin disorders.

Association Between Consanguinity and Hemoglobinopathy Type

Table 4: Cross-tabulation of Consanguinity and Disease Type

Consanguinity	*β-thalassemia (n=162)*	*SCD (n=54)*	*HbE/β (n=30)*	*p-value*
First-cousin	102 (63.0%)	27 (50.0%)	9 (30.0%)	**<0.001**
Second-cousin	33 (20.4%)	9 (16.7%)	6 (20.0%)	
Beyond	12 (7.4%)	3 (5.6%)	3 (10.0%)	
Non-consanguineous	15 (9.2%)	15 (27.7%)	12 (40.0%)	

A statistically significant association ($p < 0.001$) was found between parental consanguinity and type of hemoglobinopathy. First-cousin marriages were strongly associated with β-thalassemia major, while non-consanguineous unions showed relatively higher proportions of HbE/β-thalassemia.

Age at Diagnosis

Table 4.5: Age at Diagnosis (years)

Disease Type	*Mean ± SD*
β-thalassemia major	1.8 ± 0.9
Sickle Cell Disease	3.6 ± 1.4
HbE/β-thalassemia	4.2 ± 1.6
p-value	**<0.001**

Children with β-thalassemia major were diagnosed significantly earlier (**mean 1.8 years**) due to severe clinical presentation, while HbE/β-thalassemia cases had delayed diagnosis, reflecting milder disease phenotype.

Annual Transfusion Burden

Table 6: Annual Transfusion Requirement

Disease Type	*Mean Units/Year ± SD*
β-thalassemia major	16.2 ± 3.8
Sickle Cell Disease	5.4 ± 2.1
HbE/β-thalassemia	7.1 ± 2.5
p-value	**<0.001**

β-thalassemia patients required significantly higher transfusion support, reflecting disease severity. SCD patients required fewer transfusions, mainly during crises.

Pre-transfusion Hemoglobin Levels

Table 7: Pre-transfusion Hemoglobin (g/dL)

Disease Type	***Mean ± SD***
β-thalassemia major	7.2 ± 0.8
Sickle Cell Disease	8.4 ± 1.1
HbE/β-thalassemia	8.9 ± 1.2
p-value	**<0.001**

Lower hemoglobin levels in β-thalassemia indicate severe anemia, necessitating frequent transfusions, while relatively higher levels in HbE/β reflect milder disease.

Serum Ferritin Levels

Table 8: Serum Ferritin (ng/mL)

Disease Type	***Median (IQR)***
β-thalassemia major	2,850 (2,100–3,600)
Sickle Cell Disease	1,200 (850–1,800)
HbE/β-thalassemia	1,650 (1,100–2,200)
p-value	**<0.001**

Ferritin levels were significantly elevated in β-thalassemia due to chronic transfusion-related iron overload, highlighting the need for chelation therapy.

Vaso-occlusive Crises in SCD

Table 9: Annual VOC Episodes (n=54)

Category	***Frequency (n)***	***Percentage (%)***
0–2 episodes	18	33.3
3–5 episodes	24	44.4
>5 episodes	12	22.3

Most SCD patients experienced 3–5 crises annually, indicating moderate disease severity and substantial healthcare burden.

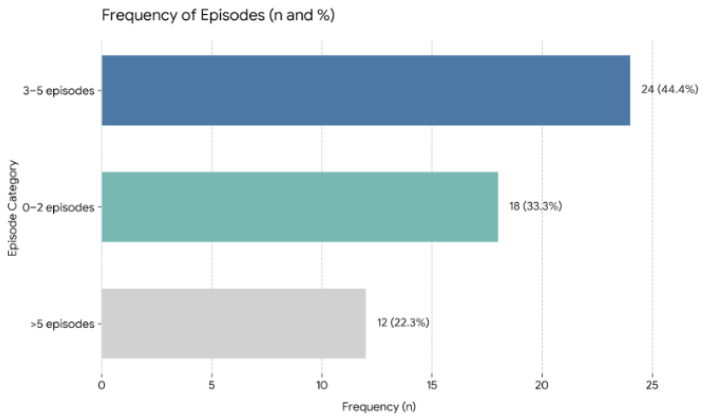


Fig 3: Annual VOC Episodes (n=54)

Multivariate Logistic Regression Analysis

Table 10: Association Between Consanguinity and β-thalassemia

Variable	Adjusted OR	95% CI	p-value
First-cousin marriage	3.8	1.9–7.4	<0.001
Second-cousin marriage	2.1	1.1–4.3	0.032
Low socioeconomic status	1.7	1.0–3.0	0.048

First-cousin consanguinity significantly increased the odds of β-thalassemia (**OR = 3.8**), even after adjusting for confounders, confirming it as a strong independent risk factor.

Multivariate Linear Regression Analysis

Table 11: Effect of Consanguinity on Clinical Outcomes

Outcome Variable	*β Coefficient*	*p-value*
Transfusion burden	+2.6	<0.001
Serum ferritin	+480 ng/mL	0.002
Hemoglobin level	−0.6 g/dL	0.011

Consanguinity was independently associated with increased transfusion needs, higher ferritin levels, and lower hemoglobin, suggesting more severe disease phenotypes among offspring of consanguineous unions.

DISCUSSION

The findings demonstrate a strong and statistically significant association between consanguineous unions particularly first-cousin marriages and the occurrence as well as severity of β-thalassemia major, sickle cell disease (SCD), and HbE/β-thalassemia. These results are consistent with emerging global and regional evidence emphasizing the genetic and clinical consequences of consanguinity in autosomal recessive disorders. A key observation of this study is the high prevalence of consanguinity (82.9%), with first-cousin marriages constituting the majority. This aligns with recent epidemiological reports from South Asia and the Middle East, where consanguinity rates range between 60–80% in affected populations [14]. Cultural, social, and economic factors contribute to the persistence of such marital practices, particularly in Pakistan, where intra-familial unions are often preferred to maintain social cohesion and inheritance structures. However, from a genetic perspective, such practices increase the probability of homozygosity for deleterious alleles, thereby elevating the burden of

inherited disorders such as hemoglobinopathies [15].

The study further demonstrated a significant association between consanguinity and β-thalassemia major, with first-cousin marriages increasing the odds by nearly fourfold (adjusted OR = 3.8). This finding corroborates previous multicenter analyses indicating that β-thalassemia is disproportionately prevalent among offspring of consanguineous unions due to the autosomal recessive inheritance pattern of β-globin gene mutations [16]. Moreover, the comparatively lower proportion of non-consanguineous cases among β-thalassemia patients reinforces the role of genetic clustering within families. Similar trends have been reported in studies from Iran, Saudi Arabia, and India, where consanguinity has been identified as a primary driver of thalassemia prevalence [17]. The distribution of sickle cell disease and HbE/β-thalassemia showed relatively higher proportions in non-consanguineous unions compared to β-thalassemia. This suggests that while consanguinity amplifies risk, population genetics, migration patterns, and ethnic variability also contribute to disease distribution [18]. HbE/β-thalassemia, for instance, is more prevalent in Southeast Asian populations, and its occurrence in Lahore may reflect demographic mixing and internal migration trends. Another important dimension explored in this study is the impact of consanguinity on clinical severity indicators. Children born to consanguineous parents exhibited significantly worse clinical outcomes, including higher transfusion requirements, lower pre-transfusion hemoglobin levels, and elevated serum ferritin concentrations. These findings suggest that consanguinity not only influences disease occurrence but may also modulate phenotypic severity. One plausible explanation is the co-inheritance of modifier genes or the presence of more severe mutation combinations within closely related gene pools [19]. The earlier age at diagnosis observed in β-thalassemia major (mean 1.8 years) is consistent with its severe clinical phenotype, characterized by profound anemia and early transfusion dependency. This observation aligns with global literature, where β-thalassemia major is typically diagnosed within the first two years of life due to symptomatic anemia [20]. In contrast, delayed diagnosis in HbE/β-thalassemia reflects its relatively milder and heterogeneous presentation, often leading to underdiagnosis or late clinical recognition. The transfusion burden analysis further highlights the clinical implications of different hemoglobinopathies. β-thalassemia patients required significantly higher annual transfusions compared to SCD and HbE/β-thalassemia. This is in agreement with established clinical guidelines, which identify regular transfusion therapy as the cornerstone of β-thalassemia management [21]. The increased transfusion frequency in consanguineous groups may indicate more severe genotypic variants, necessitating intensive clinical management. Additionally, serum ferritin levels were markedly elevated in β-thalassemia patients, particularly among those with consanguineous parentage. Chronic transfusion therapy inevitably leads to iron overload, which, if not adequately managed with chelation therapy, results in multi-organ complications. The observed association between consanguinity and higher ferritin levels may reflect increased transfusion exposure, further supporting the hypothesis of enhanced disease severity [22]. In patients with sickle cell disease, the frequency of vaso-occlusive crises (VOC) was found to be moderate, with most patients experiencing 3–5 episodes annually. While consanguinity did not show as strong an association with VOC frequency as with transfusion-dependent parameters, it may still contribute indirectly through genetic modifiers influencing disease expression. Recent studies have highlighted the role of fetal hemoglobin levels and co-inherited genetic traits in modulating SCD severity, which may be more prevalent in genetically homogeneous populations [23]. The multivariate analyses conducted in this study provide further strength to the findings by adjusting for potential confounders such as socioeconomic status and parental education. Even after adjustment, consanguinity remained an independent predictor of both disease occurrence and adverse clinical outcomes. This underscores the robustness of the observed associations and highlights consanguinity as a modifiable public health risk factor. From a public health perspective, these findings carry significant implications. The strong association between consanguinity and hemoglobinopathy burden emphasizes the urgent need for preventive strategies, including premarital screening, genetic counseling, and public awareness programs. Countries such as Cyprus and Iran have successfully implemented national thalassemia prevention programs, resulting in a substantial reduction in disease incidence [24]. Similar models could be adapted in Pakistan, taking into account local cultural

sensitivities and healthcare infrastructure.

Also the study highlights the importance of integrating genetic education into primary healthcare systems. Healthcare professionals, particularly those working in maternal and child health, should be trained to provide counseling regarding the risks associated with consanguineous marriages. Early screening programs, including neonatal screening and carrier detection, could significantly reduce the long-term disease burden [25]. Despite its strengths, including a prospective design and multicenter setting, this study has certain limitations. The absence of molecular genotyping limits the ability to correlate specific mutations with clinical severity. Additionally, the study population was limited to tertiary care centers in Lahore, which may affect generalizability to rural populations. Future studies incorporating genomic analysis and larger, population-based samples are recommended to further elucidate the genetic mechanisms underlying these associations.

Study Limitations and Future Directions

The present study, while methodologically robust and clinically informative, is not without limitations that must be acknowledged for accurate interpretation of the findings. Firstly, the study was conducted in two major tertiary care centers in Lahore, namely Sheikh Zayed Hospital Lahore and Ghurki Trust Teaching Hospital, which primarily receive referred and more severe cases. This may introduce selection bias, as the study population may not fully represent the broader community, particularly rural or underdiagnosed populations. Consequently, the prevalence and severity of hemoglobinopathies observed in this cohort may be overestimated compared to the general population. Another important limitation is the lack of molecular genetic analysis. Although diagnosis was confirmed through hemoglobin electrophoresis and HPLC, the absence of β-globin gene mutation profiling limits the ability to correlate specific genotypes with phenotypic severity. Given that hemoglobinopathies exhibit considerable genetic heterogeneity, the inability to assess mutation types and genetic modifiers restricts deeper insights into disease variability, particularly in the context of consanguinity. Additionally, reliance on self-reported consanguinity data and pedigree reconstruction may introduce recall bias or misclassification, especially in extended family structures where accurate genealogical information may be difficult to verify. The cross-sectional design, despite being prospective in data collection, also limits the ability to establish causal relationships between consanguinity and clinical outcomes. While strong associations were identified, longitudinal follow-up would be necessary to evaluate disease progression, treatment response, and long-term complications such as organ damage due to iron overload. Furthermore, certain potentially relevant variables such as adherence to iron chelation therapy, nutritional status, and access to healthcare services were not comprehensively assessed, which may act as confounding factors influencing clinical outcomes. In terms of future directions, there is a clear need for large-scale, multicenter population-based studies that include both urban and rural settings to provide a more representative epidemiological picture of hemoglobinopathies in Pakistan. Incorporating molecular diagnostics and genomic sequencing would significantly enhance the understanding of genotype–phenotype correlations and allow identification of high-risk mutations within consanguineous populations. Future research should also explore the role of genetic modifiers, such as fetal hemoglobin levels and co-inherited traits, in determining disease severity. Longitudinal cohort studies are particularly recommended to monitor disease progression, treatment outcomes, and survival patterns over time. Such studies would provide valuable insights into the long-term impact of consanguinity on morbidity and healthcare burden. Additionally, interventional research evaluating the effectiveness of premarital screening programs, genetic counseling, and public awareness campaigns is essential to translate these findings into practical public health strategies. Finally, there is a growing opportunity to integrate artificial intelligence and predictive modeling approaches in future studies to identify at-risk populations and optimize resource allocation in hemoglobinopathy management. By combining clinical, genetic, and sociodemographic data, predictive frameworks could support early diagnosis and targeted interventions, ultimately reducing the burden of these inherited disorders.

Conclusion

the present study provides compelling evidence that consanguinity is a critical determinant of both the prevalence and clinical severity of hemoglobinopathies in pediatric populations. The findings reinforce the need for targeted public health interventions and genetic counseling initiatives to mitigate the growing burden of these disorders. Addressing consanguinity as a modifiable risk factor could play a pivotal role in reducing the incidence and improving the clinical outcomes of hemoglobinopathies in Pakistan and similar high-risk regions.

Conflict of interest

The authors declared no conflict of interest.

Author Contribution

- Concept & Design of the study: *Tooba Ammar & Hussain Farooq*
- Drafting: *Nabila Akram*
- Data analysis: *Maryam Khanzada Rajput & Ujala Aymun*
- Critical Review & Final approval: *Ushna Ali & Tooba Ammar*

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the study's integrity.

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