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Original Article

Consanguineous Marriages and Thalassemia: A Study on Pre-Marital Screening; Caregiver and Family Awareness

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ABSTRACT

Background: Thalassemia remains a major preventable inherited blood disorder in Pakistan, where high carrier frequency, frequent consanguineous marriage, and limited uptake of premarital screening contribute to continued disease transmission. Objective: This study assessed caregiver awareness, cultural acceptance of cousin marriage, consanguinity patterns, family history, and willingness for premarital or future pregnancy-related screening among families of registered thalassemia patients. Methods: A descriptive cross-sectional study was conducted from June 2024 to January 2025 at the Fatimid Foundation, Shaheed Benazir Bhutto Thalassemia Centre, Larkana, Pakistan. Data were collected from 172 caregivers using a semi-structured questionnaire covering sociodemographic factors, consanguinity, family history, awareness, screening practices, cultural perception, physician counseling, age at diagnosis, and blood group. Categorical variables were analyzed using frequencies, percentages, chi-square tests, and phi correlation coefficients. Results: Consanguineous marriage was reported in 85% of families, while cultural acceptance of cousin marriage was reported in 92%. Family affected status was present in 47%. Premarital screening uptake was very low at 2%, whereas willingness for screening before future pregnancy increased to 76% after counseling. Consanguinity was significantly associated with cultural perception ($r = 0.36$, $p < 0.001$), and family affected status was associated with family history ($r = 0.37$, $p < 0.001$). Awareness showed only a weak association with screening behavior ($r = 0.21$, $p = 0.004$). Conclusion: Cultural acceptance of consanguinity and weak translation of awareness into screening behavior remain major barriers to thalassemia prevention. Physician-led counseling, cascade family screening, and culturally sensitive premarital screening programs are needed in high-risk communities. Keywords: Consanguineous marriage, Thalassemia, Caregivers, Premarital screening, Awareness.

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INTRODUCTION

Thalassemia is a major inherited hemoglobin disorder characterized by defective or reduced synthesis of α- or β-globin chains, resulting in chronic anemia, lifelong transfusion dependence in severe cases, iron overload, and substantial psychosocial and economic burden for affected families. Globally, hemoglobinopathies remain among the most common monogenic disorders, with beta-thalassemia

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major contributing significantly to childhood morbidity and preventable genetic disease burden, particularly in regions where carrier frequency is high and organized screening systems are incompletely implemented (1,2). In Pakistan, thalassemia represents a persistent public health challenge, with an estimated 5–8% carrier frequency and thousands of affected births reported annually, although the true burden is likely underestimated because many patients from rural and underserved areas remain outside formal registration systems (3,4). This burden is especially relevant in settings where access to genetic counseling, premarital carrier testing, and structured family-based screening remains inconsistent (3).

Consanguineous marriage is a well-established risk factor for autosomal recessive disorders because it increases the probability that both partners carry the same pathogenic variant inherited from a common ancestor. In Pakistan, cousin marriage is culturally accepted and widely practiced, with national estimates showing high proportions of first-cousin and second-cousin unions among married women (5–7). Although consanguinity is not the sole determinant of thalassemia transmission, its high frequency in communities with elevated carrier rates increases the probability of affected offspring when both partners are carriers. Previous Pakistani and regional evidence has linked consanguineous unions with increased reproductive risks, congenital disorders, and inherited hematological conditions, reinforcing the need for prevention strategies that are culturally acceptable rather than purely prohibitive (8–10).

Premarital screening and genetic counseling are recognized primary prevention strategies for beta-thalassemia and other inherited blood disorders. International experience from countries with structured screening programs indicates that premarital or preconception carrier identification, when combined with counseling and informed reproductive decision-making, can reduce the birth prevalence of severe hemoglobinopathies (11–17). However, the effectiveness of such programs depends not only on test availability but also on community awareness, affordability, counseling quality, family acceptance, and trust in healthcare professionals. In Pakistan and similar South Asian settings, uptake of screening remains limited despite increasing public awareness, partly because decisions about marriage and reproduction are shaped by family expectations, social norms, perceived stigma, and incomplete understanding of genetic inheritance (18–24).

A key unresolved problem is the persistent gap between knowledge and preventive behavior. Families may be aware that thalassemia is inherited, yet still avoid premarital screening because of cultural pressure, fear of disrupted marriage arrangements, financial barriers, or lack of physician-led counseling. This gap is particularly important among caregivers of children already affected by thalassemia, because these families represent a high-risk group in which awareness, family history, and future reproductive decisions intersect directly. However, limited local evidence from interior Sindh has examined how cultural acceptance of cousin marriage, consanguinity patterns, family history, caregiver awareness, and screening behavior relate to one another within families of registered thalassemia patients.

Therefore, this cross-sectional study was conducted among caregivers and family members of registered thalassemia patients at the Fatimid Foundation, Shaheed Benazir Bhutto Thalassemia Centre, Larkana, to assess awareness of consanguineous marriage risks, determine the frequency and cultural acceptability of cousin marriage, examine associations between consanguinity, family history, and affected family status, and evaluate whether physician counseling influences willingness to undergo premarital or future pregnancy-related screening. The study was guided by the hypothesis that cultural acceptance of consanguinity is positively associated with consanguineous marriage practices and familial occurrence of thalassemia, while awareness alone is insufficient to ensure preventive screening unless supported by structured counseling and accessible screening services.

MATERIAL AND METHODS

The present study was conducted as a descriptive cross-sectional study at the Fatimid Foundation, Shaheed Benazir Bhutto Thalassemia Centre, Larkana, Pakistan, a referral facility providing regular transfusion-related services to patients with thalassemia. The study was carried out from June 2024 to January 2025 and focused on caregivers and family members of registered thalassemia patients to assess awareness, perceptions, and preventive practices related to consanguineous marriage, premarital screening, hereditary transmission of thalassemia, and perceived cultural acceptability of cousin marriage (12).

Caregivers of registered thalassemia patients were eligible for inclusion if they were available during the data collection period, willing to participate, and provided informed consent. Caregivers who refused participation, were unavailable during the study period, or submitted incomplete responses were excluded. Participants were recruited through a convenience sampling approach from outpatient waiting areas during routine hospital visits. Before data collection, the study purpose was explained to each participant, confidentiality was assured, and written or verbal informed consent was obtained (13).

Data were collected through face-to-face interviews using a semi-structured questionnaire developed after review of relevant literature and adapted primarily from a previously validated study on awareness and acceptance of premarital carrier screening for thalassemia among adults in Rawalpindi and Islamabad (26). The questionnaire included sociodemographic information, age of diagnosis of the affected child, family history of thalassemia, history of consanguineous marriage, knowledge of hereditary transmission, prior premarital screening practice, awareness of cousin marriage-related genetic risk, cultural perceptions regarding cousin marriage, physician counseling at first diagnosis, willingness for screening before future pregnancy, and blood group of the affected child. Additional items relevant to the local study objectives, including physician counseling and patient blood group, were developed by the investigators (16).

The principal variables were operationalized as categorical responses. Consanguineous marriage referred to marriage between biologically related individuals, particularly first-degree or cousin unions. Family affected status referred to the presence of one or more thalassemia-affected individuals within the family. Family history referred to a reported history of thalassemia or related inherited blood disorders among relatives. Premarital screening referred to carrier screening performed before marriage, whereas screening before future pregnancy reflected intention or willingness to undergo screening after counseling. Cultural perception referred to participant-reported social acceptability of cousin marriage within the family or community context (17).

The sample size was calculated using the single-proportion formula, $n = Z^2p(1-p)/d^2$, with a 95% confidence level, expected beta-thalassemia carrier prevalence of 7% in Pakistan, and 5% margin of error. The minimum required sample size was approximately 100 participants and was increased to 120 after accounting for an anticipated 20% non-response rate. A total of 172 caregivers were ultimately recruited, exceeding the calculated requirement and improving the precision of descriptive estimates (19).

Data was entered and analyzed using IBM SPSS Statistics version 27.0.1. Categorical variables were summarized as frequencies and percentages. One-sample chi-square tests were used to assess the distribution of binary yes/no responses for individual variables, while chi-square tests of independence were applied to examine associations between key categorical variables, including consanguineous marriage and cultural perception, and family affected status and family history. Correlation patterns among binary variables were further examined using phi coefficients and displayed through heatmap-based visualization of yes responses, no responses, and comparative response patterns. Patient-related variables, including age group, age at diagnosis, and blood group, were analyzed descriptively using

frequency tables. A p-value of <0.05 was considered statistically significant. Incomplete questionnaires were excluded before analysis, and complete-case analysis was performed.

Potential sources of bias were addressed through standardized face-to-face administration of the questionnaire, use of the same core questions for all participants, and verification of eligibility before interview. Because the study used convenience sampling from a single thalassemia center, selection bias and limited generalizability were recognized as inherent design limitations. To support data integrity, completed questionnaires were reviewed for completeness before entry, categorical coding was standardized, and analysis was restricted to predefined study variables aligned with the study objectives.

Ethical approval was obtained from the Institutional Review Board of Shaheed Mohtarma Benazir Bhutto Medical University, Larkana, under approval number SMBBMU/IRB/95. Formal permission was also obtained from the administration of the Fatimid Foundation, Shaheed Benazir Bhutto Thalassemia Centre, Larkana. Participation was voluntary, no invasive procedure was performed, participants were free to withdraw at any stage, and all responses were kept confidential and used only for research purposes.

RESULTS

A total of 172 caregivers/family members of registered thalassemia patients were included in the analysis. Consanguineous marriage was highly prevalent, with approximately 146/172 participants (85%) reporting first-degree/cousin marriage practices. Cultural acceptance of cousin marriage was even higher, reported by approximately 158/172 participants (92%). Nearly half of the families, approximately 81/172 (47%), reported affected family status. In contrast, premarital screening uptake was extremely low, reported by only approximately 3/172 participants (2%), while willingness for screening before future pregnancy increased to approximately 131/172 (76%) after physician counseling.

Table 1. Descriptive Distribution of Key Study Variables Among Caregivers of Thalassemia Patients

Variable	Positive Response	Approximate n/N	Percentage	Chi-Square	p-value
Consanguineous marriage	Yes	146/172	85%	47.88	<0.001
Family affected by thalassemia	Yes	81/172	47%	0.19	0.666
Family history	Yes			21.88	<0.001
Premarital screening	Yes	3/172	2%	101.92	<0.001
Awareness of cousin marriage risk	Yes			53.57	<0.001
Cultural perception supporting cousin marriage	Yes	158/172	92%	71.07	<0.001
Screening before future pregnancy	Yes	131/172	76%	20.79	<0.001
Doctor's counseling about cousin marriage risk	Yes			24.17	<0.001

The one-sample chi-square analysis showed statistically significant response distributions for most variables, including consanguineous marriage, family history, premarital screening, awareness of cousin marriage risk, cultural perception, willingness for future screening, and doctor counseling. The only non-significant variable was family affected status ($\chi^2 = 0.19$, $p = 0.666$), indicating that the distribution of affected versus non-affected family status was not statistically different from the expected distribution. The most notable preventive gap was observed between very low premarital screening uptake (2%) and substantially higher willingness for future pregnancy-related screening (76%), suggesting that counseling may improve intention even when prior screening behavior is poor.

Table 2. Association Between Cultural, Familial, and Preventive Variables

Variable 1	Variable 2	Chi-Square	Correlation Effect Size	p-value
Consanguineous marriage	Cultural perception of cousin marriage	18.70	r = 0.36	<0.001
Family affected	Family history	21.85	r = 0.37	<0.001
Premarital screening	Awareness of cousin marriage risk		r = 0.21	0.004

Consanguineous marriage showed a statistically significant positive association with cultural acceptance of cousin marriage ($\chi^2 = 18.70$, $r = 0.36$, $p < 0.001$), indicating that participants from communities or

families where cousin marriage was culturally acceptable were more likely to report consanguineous marriage practices. Family affected status was also significantly associated with family history ($\chi^2 = 21.85$, $r = 0.37$, $p < 0.001$), suggesting clustering of thalassemia within families with prior inherited disease history. Premarital screening showed only a weak but statistically significant association with awareness of cousin marriage risk ($r = 0.21$, $p = 0.004$), supporting the interpretation that awareness alone may not be sufficient to produce preventive screening behavior.

Table 3. Age Distribution, Age at Diagnosis, and Blood Group of Thalassemia Patients

Variable	Category	n	Percentage
Current age	1–3 years	30	17.4%
	4–6 years	47	27.3%
	7–9 years	43	25.0%
	10–12 years	24	14.0%
	13–15 years	26	15.1%
	16–18 years	2	1.2%
Age at diagnosis	0–3 months	43	25.0%
	4–6 months	73	42.4%
	7–12 months	21	12.2%
	1–3 years	28	16.3%
	4–5 years	5	2.9%
	6–10 years	2	1.2%
Blood group	A positive	54	31.4%
	B positive	54	31.4%
	AB positive	14	8.1%
	O positive	44	25.6%
	A negative	2	1.2%
	B negative	3	1.7%
	O negative	1	0.6%

Most affected children were between 4–6 years (47/172, 27.3%) and 7–9 years (43/172, 25.0%), indicating that the highest observed burden was among younger pediatric patients. Diagnosis most commonly occurred between 4–6 months of age (73/172, 42.4%), followed by 0–3 months (43/172, 25.0%) and 7–12 months (21/172, 12.2%). Overall, 137/172 patients (79.6%) were diagnosed within the first year of life, reflecting early clinical recognition in most cases. Blood group distribution showed that A positive and B positive were the most frequent groups, each reported in 54/172 patients (31.4%), followed by O positive in 44/172 patients (25.6%). Rh-negative blood groups were uncommon, collectively representing only 6/172 patients (3.5%).

Table 4. Heatmap Correlation Findings for Yes, No, and Comparative Response Patterns

Response Pattern	Variable 1	Variable 2	Correlation	p-value
Yes	Consanguineous marriage	Cultural perception of cousin marriage	0.36	<0.001
Yes	Family affected	Family history	0.37	<0.001
Yes	Premarital screening	Awareness of cousin marriage risk	0.21	0.004
No	Consanguineous marriage	Cultural perception of cousin marriage	0.36	<0.001
No	Family affected	Family history	0.37	<0.001
No	Premarital screening	Awareness of cousin marriage risk	0.21	0.004
Comparative yes/no	Consanguineous marriage	Cultural perception of cousin marriage	-0.36	<0.001
Comparative yes/no	Family affected	Family history	-0.37	<0.001
Comparative yes/no	Premarital screening	Awareness of cousin marriage risk	-0.21	0.004

Heatmap-based correlation analysis confirmed consistent statistically significant relationships across response patterns. The association between consanguineous marriage and cultural perception remained moderate and significant across both yes and no response matrices ($r = 0.36$, $p < 0.001$). Similarly, family affected status and family history showed a consistent moderate association ($r = 0.37$, $p < 0.001$). The association between premarital screening and awareness was weaker but still significant ($r = 0.21$, $p = 0.004$). The negative values in the comparative yes/no matrix reflect inverse coding between response categories rather than a contradictory clinical relationship. These findings collectively indicate that

cultural acceptability and familial clustering are stronger correlates of thalassemia-related risk patterns than awareness-linked screening behavior alone.

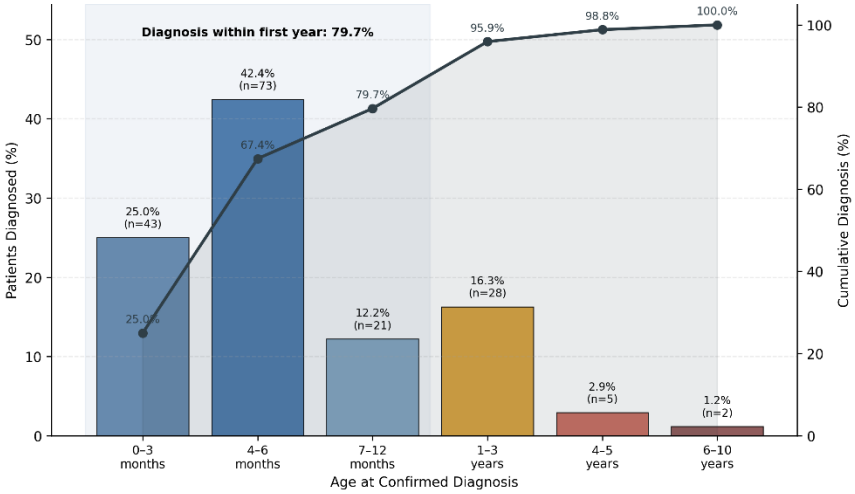

Figure 1 Timing Gradient of Thalassemia Diagnosis Among Registered Pediatric Patients

The diagnosis-timing pattern showed that 43/172 patients (25.0%) were diagnosed by 0–3 months and 73/172 (42.4%) by 4–6 months, producing a cumulative diagnosis rate of 67.4% by 6 months and 79.7% within the first year. Delayed diagnosis beyond one year accounted for 35/172 patients (20.3%), including 28/172 (16.3%) diagnosed at 1–3 years, suggesting that although early recognition predominated, a clinically meaningful subgroup still experienced delayed diagnostic confirmation.

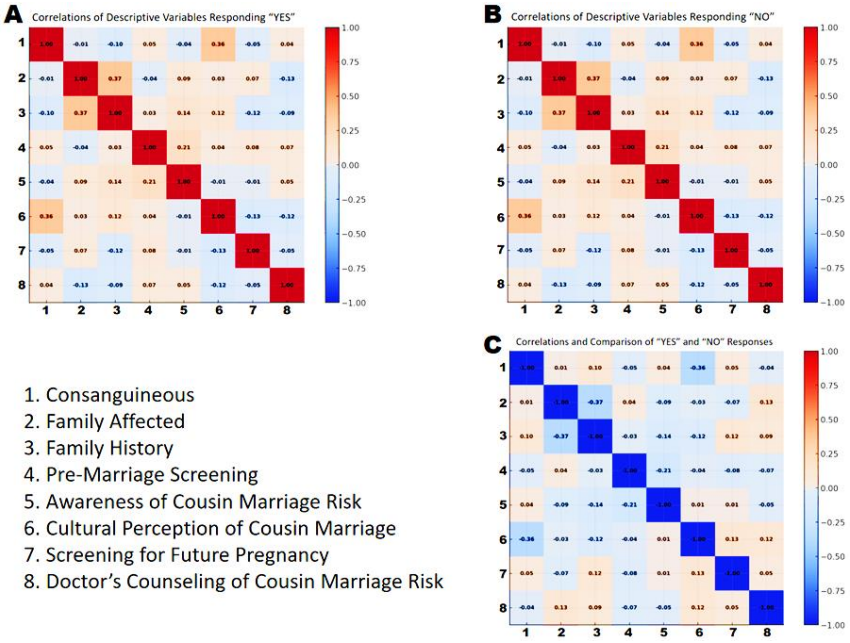

Figure 2 Heatmap Correlation Matrix of Descriptive Variables Related to Consanguinity, Family History, Screening, Awareness, Cultural Perception, and Physician Counselling.

Panel A shows correlations among variables coded as "Yes" responses, Panel B shows correlations among variables coded as "No" responses, and Panel C presents the comparative correlation pattern between "Yes" and "No" response categories. Variables are numbered as follows: 1 = Consanguineous marriage, 2 = Family affected, 3 = Family history, 4 = Premarital screening, 5 = Awareness of cousin marriage risk, 6 = Cultural perception of cousin marriage, 7 = Screening for future pregnancy, and 8 = doctor's counseling of cousin marriage risk. Red cells indicate positive correlations, blue cells indicate negative correlations, and darker color intensity reflects stronger correlation magnitude. The heatmap demonstrates that the strongest clinically relevant associations were observed between family affected

status and family history ($r = 0.37$, $p < 0.001$) and between consanguineous marriage and cultural perception of cousin marriage ($r = 0.36$, $p < 0.001$), indicating that familial clustering of thalassemia and cultural acceptance of cousin marriage are important linked factors in this population. A weaker but statistically significant association was observed between premarital screening and awareness of cousin marriage risk ($r = 0.21$, $p = 0.004$), suggesting that awareness contributes to screening behavior but does not strongly translate into preventive practice. The mirrored pattern in Panels A and B confirms consistency across affirmative and negative response coding, while the negative coefficients in Panel C reflect inverse coding between "Yes" and "No" categories rather than a contradictory clinical association. Overall, the correlation structure supports the interpretation that cultural acceptability and family history are stronger determinants of thalassemia-related risk patterns than awareness-linked screening behavior alone.

DISCUSSION

This study demonstrates that consanguineous marriage remains highly prevalent among families of registered thalassemia patients in Larkana and is closely linked with cultural acceptability of cousin marriage. The observed association between consanguineous marriage and cultural perception of cousin marriage ($r = 0.36$, $p < 0.001$) indicates that marriage practices in this population are not shaped by individual preference alone but are embedded within broader family and community norms. This finding is consistent with previous evidence from Pakistan and other high-consanguinity regions, where cousin marriage has been repeatedly associated with increased transmission of autosomal recessive disorders, including beta-thalassemia (27–31). The high proportion of first-degree consanguineous unions in the present study reinforces the need to frame prevention strategies around informed reproductive decision-making rather than culturally insensitive discouragement of traditional marriage practices.

The significant association between family affected status and family history ($r = 0.37$, $p < 0.001$) further supports the familial clustering of thalassemia in high-risk households. This finding is biologically plausible because thalassemia follows an autosomal recessive inheritance pattern, and repeated intra-family marriages increase the probability that both partners carry the same pathogenic variant. Earlier Pakistani studies have similarly reported high rates of parental consanguinity among children with thalassemia and have shown that even when affected families possess basic awareness of the disease, preventive action is often not taken before marriage or conception (32–36). These results suggest that family history should be used as a practical entry point for cascade screening, carrier identification, and counseling of siblings and extended relatives.

A key finding of this study is the major gap between awareness and preventive behavior. Premarital screening uptake was extremely low, although willingness for screening before future pregnancy increased substantially after counseling. The weak but statistically significant association between awareness of cousin marriage risk and premarital screening ($r = 0.21$, $p = 0.004$) suggests that awareness alone is insufficient to produce preventive action. This pattern is consistent with previous research from Pakistan and other countries showing that knowledge of thalassemia does not necessarily translate into screening behavior when social pressure, stigma, financial barriers, limited counseling, and fear of disrupted marriage arrangements remain unaddressed (14,23,24,36,37). Therefore, public health strategies should move beyond general awareness campaigns and prioritize structured, family-centered genetic counseling delivered in culturally acceptable language.

The finding that physician counseling was associated with greater willingness for future screening highlights the central role of healthcare professionals in thalassemia prevention. International experience shows that premarital screening programs are more effective when testing is accompanied by counseling, risk communication, and accessible follow-up services (38,39,43,44). However, in Pakistan, screening implementation remains inconsistent and is often limited by fragmented services, lack of

trained genetic counselors, and poor integration of preventive counseling into routine clinical encounters. The current findings support the need for physician-led counseling at the time of diagnosis and during follow-up visits, particularly for families with multiple children, positive family history, or planned future pregnancies (41).

The age-at-diagnosis pattern also has important clinical implications. Most patients were diagnosed within the first year of life, particularly between 4–6 months, which is consistent with the clinical course of beta-thalassemia major as fetal hemoglobin declines and anemia becomes clinically evident. However, approximately one-fifth of patients were diagnosed after one year of age, indicating that delayed recognition remains present in a clinically meaningful subgroup. Delayed diagnosis may postpone transfusion planning, iron overload surveillance, family counseling, and carrier testing among relatives. Early identification through newborn screening, family-based carrier screening, and improved referral pathways may therefore reduce diagnostic delay and improve long-term management (39).

The blood group distribution showed higher proportions of A positive and B positive blood groups, followed by O positive, while Rh-negative groups were uncommon. These findings should be interpreted descriptively rather than causally, because blood group distribution in this hospital-based sample may reflect background population blood group frequencies rather than any biological association with thalassemia. The inclusion of blood group data remains useful for transfusion service planning, but it should not be presented as a risk factor for disease occurrence without population-level comparative analysis.

This study has several limitations. First, it was conducted at a single thalassemia center and included only caregivers of already registered patients, limiting generalizability to the wider community. Second, the use of convenience sampling may have introduced selection bias, as families regularly attending the center may differ from those with poor healthcare access. Third, the cross-sectional design allows identification of associations but cannot establish causality. Fourth, self-reported data on screening behavior, family history, and cultural perception may be affected by recall or social desirability bias. Despite these limitations, the study provides useful local evidence from a high-risk population and identifies modifiable gaps in counseling, screening uptake, and family-centered prevention (29-36). Overall, the findings indicate that thalassemia prevention in Pakistan requires an integrated model combining premarital screening, cascade family screening, physician-led counseling, and community-sensitive education. Policies that focus only on awareness may have limited impact unless they address the social and practical barriers that prevent families from acting on genetic risk information. A culturally competent national prevention strategy, particularly in underserved regions such as interior Sindh, could reduce avoidable thalassemia births while respecting family structures and community values.

CONCLUSION

This study concludes that consanguineous marriage remains highly prevalent among families of thalassemia patients in Larkana and is significantly associated with cultural acceptance of cousin marriage and familial clustering of disease. Although awareness of genetic risk showed a statistically significant relationship with premarital screening, the association was weak, indicating that knowledge alone does not reliably translate into preventive behavior. The extremely low uptake of premarital screening, contrasted with increased willingness for future screening after counseling, highlights the importance of physician-led genetic counseling, family-based education, and accessible premarital or preconception carrier screening services. Strengthening culturally sensitive prevention programs, particularly in high-risk and underserved communities, may reduce the future burden of thalassemia and improve informed reproductive decision-making among affected families.

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