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Descriptive Epidemiology And Clinical Attributes Of Beta-Thalassemia In Upper Sindh Region Of Pakistan

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Abstract

Objective: Thalassemia is a hereditary blood disorder that affects hemoglobin synthesis, leading to anemia and other complications. This study investigated the demographic, clinical, therapeutic, and familial characteristics of beta-thalassemia patients from the upper Sindh region of Pakistan.

Methods: Through an observational cross-sectional study design, thalassemia patients registered at local hospitals and transfusion centers in upper Sindh, Pakistan, were enrolled. For enrollment from rural areas, random door-to-door surveys were carried out. A structured proforma was used to collect information, and descriptive statistics were employed.

Results: Of the 360 patients from independent families recruited (58% males, 42% females), 88% were diagnosed with thalassemia major and 12% with thalassemia minor. Majority of the patients with thalassemia major were up to the age of 5 years ($p<0.0001$) and with low body weight ($p<0.0001$); and majority received first transfusion within first year of life ($p<0.0001$). Iron overload was prevalent in 86% of patients; conversely, however, only 4% of patients were receiving iron chelation therapy. The patients had 106 affected siblings and a total of 152 thalassemia-related mortalities were reported across 94 families. Pedigree analysis revealed recurring losses within families highlighting the severe impact of the disease and the limitations of current medical interventions.

Conclusion: This cohort study illustrates the extensive socio-economic, familial, and clinical challenges faced by transfusion-dependent thalassemia patients, particularly those from rural, low-income communities in Pakistan. This research highlights the necessity for preventive public health measures, such as genetic counseling and community education to mitigate the long-term impacts of thalassemia within vulnerable populations.

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Introduction

Thalassemia is the most common form of hereditary anemia, caused by defective synthesis of one of the two globin chains (alpha or beta) in hemoglobin.[1,2] Beta-thalassemia, caused by mutations in the beta-globin gene, occurs in three main types: Thalassemia major (T.major); Thalassemia intermedia (T.intermedia); and Thalassemia minor (T.minor).[3] The clinical signs of beta-thalassemia include pale skin, expansion of bone marrow spaces, hepatosplenomegaly, extramedullary hematopoiesis, jaundice, and abdominal distension due to hepatosplenomegaly and anemia In inadequately treated patients, the most notable features include skin pigmentation, poor muscle development, genu valgum, deformities of the long bones, and craniofacial alterations such as skull bossing, a depressed nasal bridge, a mongoloid slant of the eyes, and maxillary hypertrophy.[3,4]

Beta-thalassemia is most common in tropical and subtropical regions with an estimated prevalence 1–20%. [2] Beta-thalassemia has an estimated 80–90 million carriers worldwide, representing about 1.5% of the global population.[5] In Pakistan, it affects 5–7% of the population, making the country home to the highest number of thalassemia patients dependent on blood transfusions.[6] Like other recessive disorders, the high incidence and prevalence of thalassemia in Pakistan are linked to factors such as consanguineous marriages, low income, lack of awareness, and high birth rates.[7] Thalassemia patients in Pakistan have a short life expectancy, and the high mortality rate is due to poor iron load control, high treatment costs, lack of awareness, illiteracy, and limited access to medical care.[6] In Pakistan, the situation regarding beta-thalassemia is concerning due to the high rate of cousin marriages, extended families, poor management and the lack of a national screening program.[5] The majority of these couples belong to low-income populations with little to no access to screening facilities.[5] While premarital testing laws have been passed in the provinces of Sindh, Khyber Pakhtunkhwa, and Balochistan, enforcing these regulations at the provincial level remains challenging.[6] There is no regional data available on the status of beta-thalassemia in the upper Sindh region of Pakistan. Towards this end, the current study focuses on upper Sindh, Pakistan, to provide region-specific data on the phenotypic characteristics, clinical outcomes, and family history of thalassemia. This is important because regional variations in genetic, cultural, and socioeconomic factors can influence the presentation and management of the disease.

Materials And Methods

Ethical approval and study design: The study protocol was approved by the ethical review committee of Quaid-i-Azam University, and all participants were recruited by the Helsinki-II declaration. This descriptive clinic-epidemiological study aimed to observe the prevalence pattern of beta-thalassemia in upper Sindh regions of Pakistan (Figure 1).

Sample size for rare disorders was calculated through the sample size formula for proportion estimation. A total of 360 thalassemic patients from independent families were retrospectively enrolled in a multi-center study, with recruitment from various tertiary care hospitals including the Sukkur Blood and Drug Donating Society (SBDDS) Hospital, Sukkur, and door-to-door surveys during 2019-2020. Beta-thalassemia patients who had permanent residences in the upper Sindh region were enrolled. Patients with confirmed diagnosis of beta-thalassemia based on laboratory tests, such as electrophoresis, complete blood count and microcytic hypochromic anemia were included. Only those patients were included who (or their legal guardians) provided informed verbal consent for their voluntary participation in the study. Patients with other types of anemia, incomplete medical record or other severe comorbid conditions were not included. Patients providing incomplete information or failed to appear in at least 2 follow-up visits were not enrolled. Demographic, clinical, pathological, and phenotypic data were collected using a structured proforma, along with detailed information on transfusion history and thalassemia-related complications. For each patient, a three-generation pedigree was constructed and several affected and thalassemia-related mortalities were calculated. Data were recorded and maintained in MS-Excel. Exploratory data analyses scheme was adopted, descriptive summaries were generated, and Chi-square test statistics were applied to assess the independence of variables. The data were statistically analyzed using GraphPad Prism software, version 5.00.

Results

Sample characteristics:

A total of 360 transfusion dependent patients were recruited and followed for six months. There was high preponderance of affected males compared to females (58% vs. 42%; p=0.052) (Table 1). The major cohort of patients falls in age range of 0.1-5 years (54%); the majority originated from Sukkur district (54%), rural areas (55%), spoke Sindhi language (76%), and belonged to a poor socio-economic background (56%).

Table 1: Distribution of patients concerning demographic variables

Parameter	Male, No. (%)	Female, No. (%)	Total, No. (%)
Age categories (year)			
0.1-5	102 (49)	70 (46)	172 (48)
>5-10	74 (36)	60 (39)	134 (37)
>10	31 (15)	23 (15)	54 (15)
Sum	**207 (58)**	**153 (42)**	**360 (100)**
χ^2=0.513; p=0.774; Not Sig.			
District			
Sukkur	111 (54)	84 (55)	195 (54)
Khairpur	40 (19)	30 (20)	70 (19)
Ghotki	18 (9)	15 (10)	33 (9)
Shikarpur	24 (12)	17 (11)	41 (11)
Others	14 (7)	7 (5)	21 (6)
χ^2=0.888; p=0.9262; Not Sig.			
Rural/urban origin*			
Rural	124 (60)	74 (48)	198 (55)
Urban	83 (40)	79 (52)	162 (45)
χ^2=4.731; p=0.034; Sig.			
Mother tongue			
Sindhi	160 (77)	113 (74)	273 (76)
Saraiki	28 (14)	22 (14)	50 (14)
Balochi	14 (7)	6 (4)	20 (6)
Others	5 (2)	12 (8)	17 (5)
χ^2=6.950; p=0.074; Not Sig.			
Economic quartile			
Poor	116 (56)	84 (55)	200 (56)
Low	58 (28)	39 (25)	97 (27)
Low mid	34 (16)	30 (20)	64 (18)
χ^2=0.729; p=0.694; Not Sig.			
Paternal occupation			
Govt. Servant	33 (16)	23 (15)	56 (16)
Shopkeeper	22 (11)	24 (16)	46 (13)
Labor	97 (47)	71 (46)	168 (47)
Others	55 (27)	35 (23)	90 (25)
χ^2=3.276; p=0.513; Not Sig.			

*differences in the distribution were statistically significant

Familial attributes and clinical consequences:

In this cohort, the majority of the patients were suffering from T.major (88%) while 12% had T.minor. Further analyses showed that a positive family history of thalassemia was observed in 30% of cases (Table 2). A significant proportion of patients had parental consanguineous marriages (81%). There were statistically no significant differences in the distributions of male and female patients concerning maternal age, paternal age, parity and number of affected sibs. The patients had 106 affected sibs and there were 94 thalassemia-related mortalities in these families (Table 2). The male patients had a high likelihood of having an affected sister (56%) compared to female

patients who had high likelihood of having affected brothers (55%). The differences in the distribution were, however, statistically not significant (p=0.34).

Table 2: Familial attitudes and clinical consequences among patients

Parameter	Male, No. (%)	Female, No. (%)	Total, No. (%)
Thalassemia type			
T.major	186 (90)	131 (86)	317 (88)
T.minor	21 (10)	22 (14)	43 (12)
Sum	207 (58)	153 (43)	360 (100)
χ^2=0.747; p=0.387; Not Sig.			
Family history of thalassemia			
Yes	63 (30)	44 (29)	107 (30)
No	144 (70)	109 (71)	253 (70)
χ^2=0.118; p=0.731; Not Sig.			
Parental relationship			
Consanguineous	167 (81)	124 (81)	291 (81)
Non-consanguineous	40 (19)	29 (19)	69 (19)
χ^2=0.475; p=0.788; Not Sig.			
Maternal age (years)			
Up to 30	145 (70)	114 (75)	259 (72)
>30	62 (30)	39 (25)	101 (28)
χ^2=0.868; p=0.352; Not Sig.			
Paternal age (years)			
Up to 30	104 (50)	79 (52)	183 (51)
>30	103 (50)	74 (48)	177 (49)
χ^2=0.068; p=0.794; Not Sig.			
Patients' parity			
1	37 (18)	34 (22)	71 (20)
2	48 (23)	25 (16)	73 (20)
3-5	76 (37)	63 (41)	139 (39)
>5	46 (22)	31 (21)	77 (22)
χ^2=3.569; p=0.467; Not Sig.			
No. of affected sibs			
Brothers	26 (44)	26 (55)	52 (49)
Sisters	33 (56)	21 (45)	54 (51)
Sum	59 (56)	47 (44)	106 (100)
χ^2=1.325; p=0.249			
Thalassemia-related mortalities in all families#	101 (66)	51 (34)	152 (100)

94 patients/families had a total of 152 mortalities.

Thalassemia types:

Table 3 highlights the demographic and transfusion-related attributes of T.major and T.minor patients. There was a high likelihood that T.major patients originated from rural areas (56%), compared to T.minor patients who had slightly higher likelihood of coming from urban areas (53%). T.major patients had significantly high likelihood of early registration compared to T.minor (Table 3). Likewise, T.major patients had an early age of diagnosis and the start of first transfusion compared to T.minor patients. The majority of T.major patients received their first transfusion within the first year of age (88%) as compared to T.minor patients who received their first transfusion at age 3 years or beyond. Majority of the patients from both groups T.major and T.minor received transfusion within 15-30 days interval.

Table 3: Demographic and transfusion-related attributes of thalassemia major and minor

Variables	T.major, No. (%)	T.minor, No. (%)	Total, No. (%)
Age categories (years)*			
0.1-5	166 (52)	6 (14)	172 (48)
>5-10	112 (35)	22 (51)	134 (37)
>11	39 (12)	15 (35)	54 (15)
Sum	**317 (88)**	**43 (12)**	**360 (100)**
χ^2=27.11; p<0.0001; Sig.			
Rural/urban origin			
Urban	139 (44)	23 (53)	162 (45)
Rural	178 (56)	20 (47)	198 (55)
χ^2=1.422; p=0.233; Not Sig			
Registry in the thalassemia center (years)*			
0.5	27 (9)	0	27 (8)
1	125 (39)	0	125 (35)
2	87 (27)	0	87 (24)
3	27 (9)	7 (16)	34 (9)
5	29 (9)	15 (35)	44 (12)
6-10	18 (6)	15 (35)	33 (9)
>11	4 (1)	6 (14)	10 (3)
χ^2=112.5; p<0.0001			
Age of diagnosis (years)*			
0.5	140 (44)	0	140 (39)
1	140 (44)	0	140 (39)
2	37 (12)	0	37 (10)
3	0	24 (56)	24 (7)
>3	0	19 (44)	19 (5)
χ^2=360; p<0.0001			
First transfusion (years)*			
0.5	140 (44)	0	140 (39)
1	140 (44)	0	140 (39)
2	37 (12)	0	37 (10)
3	0	24 (56)	24 (7)
>3	0	19 (44)	19 (5)
χ^2=360; p<0.0001			
Transfusion interval (days)			
7-14	10 (3)	2 (5)	12 (3)
15-30	298 (94)	41 (95)	339 (94)
>30	9 (3)	0	9 (3)
χ^2=1.482; p=0.476; Not Sig.			
Body weight at registry (kg)*			
1-10	276 (87)	10 (23)	286 (79)
11-20	40 (13)	31 (72)	71 (20)
>21	1 (0)	2 (5)	3 (1)
χ^2=95.86; p=<0.0001; Sig.			

*differences in the distributions were statistically significant; T. = thalassemia

Clinical characteristics of patients with thalassemia major and minor are presented in Table 4. Majority of T.major and T.minor patients (86%) had an iron overload which is within 1600-3000µg. Likewise, 9% had more than 3000 µg iron levels, proposing excessive iron load and high risk of organ damage. There were only 4% of individuals who were receiving chelation therapy. Infections related to hepatitis B virus (HBV) and other types were witnessed in 6% and 3% of cases, respectively. Characteristic clinical complications of thalassemia like pale and anemic appearance, arrhythmias and shortness of breath, bone deformities, swollen abdomen, liver problems and hepatomegaly, splenomegaly, and growth deficiency were evident in a large number of the patients and these complications were increasing with increasing age (data not shown). In addition, the patients had psychosocial issues and poor quality of life.

Table 4: Clinical attributes of thalassemia major and minor

Variables	T.major, No. (%)	T.minor, No. (%)	Total, No. (%)
Iron level (µg)			
<1500	16 (5)	2 (5)	18 (5)
1600-3000	273 (86)	38 (88)	311 (86)
>3000	28 (9)	3 (7)	31 (9)
χ^2=0.186; p=0.911; Not Sig.			
Chelation therapy			
Yes	13 (4)	2 (5)	15 (4)
No	304 (96)	41 (95)	345 (96)
χ^2=0.029; p=0.865; Not Sig.			
Hepatitis B virus infection			
Yes	19 (6)	2 (5)	21 (6)
No	298 (94)	41 (95)	339 (94)
χ^2=0.124; p=0.724; Not Sig.			
Other infections*			
Yes	7 (2)	4 (9)	11 (3)
No	310 (98)	39 (91)	349 (97)
χ^2=6.433; p=0.011; Sig.			
Thalassemia-related mortalities in all families#	136 (89)	16 (11)	152 (100)

*differences were statistically significant; # 94 patients/families had a total of 152 mortalities.

Thalassemia-related mortalities:

There were a total of 152 thalassemia-related mortalities, witnessed among 94 families (Table 2). Pedigree analyses revealed that there were three families with 5 mortalities each, three families with four mortalities each, 8 families with 3 mortalities, 21 families with 2 mortalities, and 59 families with one mortality (data not shown). Further, the majority of the mortalities were observed in cases with T.major (89%) (Table 4).

Discussion

This study reports demographic, clinical and transfusion-related attributes of thalassemia patients from the interior Sindh region of Pakistan. Overall, there was a high preponderance of male patients as compared to females in this study. Tuo et al.[8] reported a high incidence of thalassemia in males in the Chinese population. A recent study on the global and national burden of thalassemia by Tuo et al.[8] revealed that the prevalence rates of thalassemia among males was higher than females up to the age of 35, after which it was lower until the age of 69. Contrary to this, Lee et al.[2] found this more prevalent among females as compared to males in the Korean population. The researchers further showed that prevalence of thalassemia in female patients was consistently higher as compared to males (female-to-male ratio: 1.7–2). The authors, however, remarked that the incidence rate of thalassemia varied over time. It was concluded that increased prevalence of thalassemia in female patients could be due to the ascertainment bias, as females are prone to seek medical attention.

Children of age less than 5 years constitute the largest cohort affecting males and females equally.[8] Likewise, in the present study there were only 15% of patients with age 10 years or higher. This may depict high mortality and low life expectancy in a developing country like Pakistan. On the contrary, Lee et al.,[2] carried out a population-based study on thalassemia in Korea and observed the 13-year trend of the epidemiologic profiles and risk of comorbidities in thalassemia. The researchers witnessed thalassemia patients in all age strata and observed increased incidence of disease with increasing age in the Korean population, showing increased life expectancy and good quality of life among the patients of a developed country. Furthermore, in the current cohort, T.major was relatively more prevalent in the rural population of the district and with low socio-economic background as compared to T.minor,

which was rather more common in patients originating from urban areas. Manzoor et al.,[9] reported a high proportion of T. major patients from urban areas. Faizan et al.,[10] witnessed prevalence of T.minor in rural population of Khyber Pakhtunkhwa, Pakistan.
Parental consanguinity is known to be a risk factor for several recessively segregating disorders in inbred populations like Pakistan.[7,11,12] High incidence of parental consanguinity (81%) was evident in this cohort. This observation is concordant with other studies reported from Pakistan and other parts of the world.[13] Increased rate of parental consanguineous marriages in thalassemia patients was observed by Masih et al.,[14] and Saleem et al.,[15] in Punjab province of Pakistan. Aziz et al.[16] recruited 200 patients from Sargodha, Pakistan and revealed that 76% had parental consanguinity.
Furthermore, an estimated 30% of the recruited patients had a positive family history of thalassemia. There were at least 152 thalassemia-related mortalities among 94 families, which is quite high compared with the international scenario. With the advancements in improved management strategies, the quality of life and overall life expectancy have dramatically increased in developed nations.[2]
In the current analyses, the first and second parity were observed in 20% cases each. On the other hand, in the cohort of thalassemia patients reported by Masih et al., 34% of patients had first parity followed by 24% with second parity.[14] Parity has been shown to influence the occurrence of certain morbidities. However, its association with thalassemia remains less appreciated. An interesting finding is the prevalence of disease in young parents of age up to 30 years as compared to more paternal age cases. As opposed to Manzoor et al.[9] observed more thalassemia cases with paternal age > 30 years. T.major is diagnosed within 1 year of age in patients as compared to late diagnosis of T.minor around age 3 or later years.[17] Likewise, such patients receive first transfusion within the first year of age while T.minor patients usually receive first transfusion after 3 years of age.[18] If transfusion intervals are observed, the majority of the T.major patients receive frequent transfusions within 7-14 days, with the second one receiving within 30 days. However, T.minor patients receiving the first one within 15-30 days.
Transfusion dependent patients have a high risk of acquiring infections. In the present cohort, 6% of patients had HCV infection. In a study conducted in the Bannu district of Pakistan. 8% of patients were infected with HCV. On the other hand, in a cohort of thalassemia patients recruited from Rawalpindi, Pakistan, 49% were positive for HCV and 3% for HBV.[13] Waheed et al,[19] carried out a systematic review and meta-analysis on the incidence of HCV and hepatitis B Virus (HBV) among T. major Patients in Pakistan. There was wide variation in the infection rates among the patients from different origins. This study revealed that the overall pooled prevalences of HCV and HBV were 30% and 4%, respectively. The authors concluded that further studies were warranted to estimate the actual frequency of HBV and HCV in thalassemia patients across the country. One of the major complications for thalassemia patients receiving frequent transfusions is management of iron overload.[3] In the present cohort, the majority of patients had excessive iron load. Possible care mechanism or management is chelation therapy to control iron overload.[4] While in the current study, a very small proportion of patients are receiving it, justifying the importance of a proper mechanism for this therapy in this region

Conclusion

Remarkably high rate of parental consanguinity is associated with thalassemia in the study population. Thalassemia patients have a very high iron overload rendering them at high risk of other morbidities. The low occurrence of thalassemia in higher age groups is an indicator of low life expectancy and high mortality associated with thalassemia. It signifies the development of proper thalassemia management and prevention centers in Pakistan, where patients/families could be educated about prenatal screening, increased incidence due to inter-cousin marriages and therapeutic measures. Current study also reiterates the provision of chelation therapy and medical interventions for thalassemia patients with rural and low socio-economic backgrounds

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