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Morbidity Profile, Familial Aggregation, and Survival Challenges in Transfusion-Dependent Thalassemia: Evidence from Rawalpindi/Islamabad and Potohar Region, Pakistan

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ABSTRACT

OBJECTIVE: To explore the clinical characteristics, transfusion-related complications, and age distribution patterns suggestive of survival challenges among_BTM patients in Islamabad / Rawalpindi and the Potohar region.

METHODOLOGY: A cross-sectional, multi-centric study was conducted from January to June 2025, following ethical approval from Quaid-e-Azam University, Islamabad. A total of 497 BTM patients were identified from transfusion centers and door-to-door surveys. Convenience sampling was employed to recruit confirmed transfusion-dependent BTM cases. Data on clinical presentation, treatment history, and transfusion-related parameters were recorded. Participants with coexisting hemoglobinopathies or incomplete clinical records were excluded. Data were analyzed using GraphPad Prism (version 5.00). Additionally, qualitative insights were obtained from caregivers' and clinicians' perspectives on survival trends and a literature review of Pakistani studies.

RESULTS: This cohort comprised 56% males and 44% females, with 36% aged 5–9 years and only 6% aged≥20 years. Clinical manifestations ranged from mild (jaundice: 50%) to severe complications (anemia: 64%, recurrent infections: 34%). Chronic morbidities were frequent, notably iron overload (83%) and splenomegaly (54%). Eight percent of patients required blood transfusions every 15–30 days. Forty-one percent of the patients were infected with hepatitis B/C, and 88% were receiving chelation therapy. Familial aggregation was common: 71% had parental consanguinity, 43% had multiple affected relatives, and 29% of cases reported thalassemia-related mortalities.

CONCLUSION: This study underscores the disease burden, complications, and survival challenges
among Pakistani BTM patients, highlighting the need for improved disease management, timely chelation and better healthcare access.

KEYWORDS: Thalassemia, iron overload, splenomegaly, premature mortality, consanguinity, epidemiology

INTRODUCTION

Thalassemia is a hereditary blood disorder characterized by defective hemoglobin synthesis, leading to chronic hemolytic anemia and multiple complications[1,2]. Beta-thalassemia, caused by mutations in the β-globin gene, manifests in three forms: major, intermedia, and minor[1,3]. Beta-thalassemia major (BTM), the most severe type, presents with life-threatening anemia in infancy and requires lifelong blood transfusions for survival.[2,3]

Globally, thalassemia is one of the most common monogenic disorders, with about 1.5% of the population carrying mutations and over 300,000 severely affected children born annually. Its burden is concentrated in the Mediterranean, the Middle East, and South Asia, with Pakistan among the worst-affected countries[4-6]. The estimated carrier frequency of 5–7% translates to nearly 10 million carriers nationwide, making thalassemia a pressing public health challenge with profound socioeconomic implications.[5]

In Pakistan, multiple factors cause the high prevalence of thalassemia. Chief among these is the high rate of consanguineous marriages, which markedly increases the likelihood of homozygous inheritance.[7,8] Limited awareness, lack of genetic counseling, and the absence of a national premarital screening program further fuel new cases[7,9]. Consequently, the country hosts more than 100,000 transfusion-dependent patients, one of the largest such populations worldwide[10].

In Pakistan, the clinical management of BTM is suboptimal, and transfusion-transmitted infections remain common[10,11]. Survival outcomes are poor. Several Pakistani studies have reported shortened life expectancy, with many patients dying before adulthood due to delayed diagnosis, irregular transfusions, and limited access to specialized care[12,13]. Hence, compared with countries where comprehensive prevention and care programs exist, Pakistani patients face disproportionately higher morbidity and premature mortality.

Although regional studies have explored the clinical and pathological aspects of thalassemia, data from Rawalpindi/Islamabad and the Potohar plateau of Pakistan remain scarce.

The present study addresses this gap by assessing the clinical characteristics, transfusion-related complications, and survival patterns of BTM patients.

METHODOLOGY

A descriptive, multicentric and cross-sectional study was conducted from January to June, 2025. Ethical approval was secured from Quaid-e-Azam University, Islamabad (No. DAS/19-), and the study adhered to the principles of the Declaration of Helsinki. Informed verbal consent was obtained from parents or legal guardians in the case of minors, in accordance with protocols for vulnerable populations and low-literacy settings. Individuals with beta-thalassemia major (BTM) were recruited from transfusion centers in Rawalpindi/Islamabad and the Potohar region. Subjects were also identified through door-to-door outreach in rural and semi-urban areas. Recruitment of patients involved both institution-based and community-based strategies to ensure a diverse and representative sample.

Patients with a confirmed diagnosis of BTM, established by haematological indices and haemoglobin electrophoresis, and receiving regular blood transfusions as part of standard management were included in the study. Patients with coexisting hemoglobinopathies, inconclusive diagnostic status, or incomplete clinical records were excluded. Data were collected on biodemography, clinical and pathological presentation, socio-demographic profile, treatment history, transfusion records, and post-transfusion complications.

Data were analyzed using GraphPad Prism (version 5.00). Descriptive statistics summarized socio-demographic and clinical profiles. Associations between categorical variables were assessed using the Chi-square test. Odds ratios of affected males with 95% confidence intervals were calculated against those of affected females.

In the second tier, this study employed a qualitative exploratory design to investigate the perceived causes of reduced life expectancy among thalassemia patients. Data were collected through key informant interviews with five healthcare professionals working at the thalassemia and blood transfusion centres in Rawalpindi/Islamabad and the Potohar region. Participants included clinicians and transfusion specialists with extensive experience in the management of beta-thalassemia patients. Semi-structured discussions were conducted to capture their insights regarding factors contributing to mortality and complications in thalassemia patients. The responses were reviewed and compared with existing data trends to identify common themes and patterns.

RESULTS

Sample characteristics

A total of 497 transfusion-dependent BTM patients were enrolled in the study. Males were more frequently represented than females (56% vs. 44%). The largest proportion of patients belonged to the 5–9 year age group (36%), while only 6% were aged ≥20 years, reflecting reduced survival or higher mortality with advancing age. In terms of geographic origin, nearly half of the participants were from Punjab (49%), followed by Khyber Pakhtunkhwa (23%). More than half of the cohort resided in urban areas (54%), and a considerable proportion were from low-income families (43%) (**Table I**).

Table I: Demographic attributes of subjects with respect to gender

Variables	Male, No. (%)	Female, No. (%)	Total, No. (%)	OR#	95% CI
Age categories (year)					
0–4	55 (19)	41 (18)	96 (19)	1.05	0.67-1.65
5–9	110 (39)	72 (33)	182 (36)	1.30	0.90-1.88
10–14	66 (23)	67 (30)	133 (26)	0.69	0.46-1.03
15–19	30 (10)	24 (11)	54 (10)	0.97	0.55-1.71
≥20	19 (6)	13 (5)	32 (6)	1.14	0.55-2.36
Total	**280 (56)**	**217 (44)**	**497 (100)**		
χ^2=3.85; p=0.43					
Geographic location					
Punjab	133 (47)	113 (52)	246 (49)	0.83	0.58-1.18
Khyber Pakhtunkhwa	69 (24)	46 (21)	115 (23)	1.22	0.80-1.86
Islamabad/Rawalpindi	67 (23)	42 (19)	109 (21)	1.31	0.85-2.02
Kashmir	11 (3)	16 (7)	27 (5)	0.51	0.23-1.12
χ^2=4.98; p=0.17					
Origin					
Urban	153 (55)	114 (53)	267 (54)	1.09	0.76-1.56
Rural	127 (45)	103 (47)	230 (46)	0.92	0.64-1.32
χ^2=0.22; p=0.64					
Caste-system					
Awan	44 (16)	33 (15)	77 (16)	0.86	0.55-1.33
Rajput	31 (11)	24 (11)	55 (11)	1.04	0.64-1.70
Malik	12 (4)	9 (4)	21 (4)	1.00	0.57-1.76
Mughal	10 (4)	8 (4)	18 (4)	1.03	0.43-2.49
Qureshi	10 (4)	8 (4)	18 (4)	0.97	0.38-2.50
Jutt	8 (3)	7 (3)	15 (3)	0.97	0.38-2.50
Others	149 (53)	120 (56)	269 (54)	0.88	0.31-2.47
χ^2=0.14; p=1.00					

Economic quartile					
Poor	35 (13)	27 (12)	62 (13)	0.82	0.40-1.70
Low	121 (43)	94 (43)	215 (43)	1.00	0.70-1.43
Low-mid	48 (17)	30 (14)	78 (16)	1.29	0.79-2.12
Mid	60 (21)	51 (24)	111 (22)	0.89	0.58-1.36
High-mid/high	16 (6)	15 (7)	31 (6)	1.01	0.59-1.73
χ^2=1.38; p=0.85					

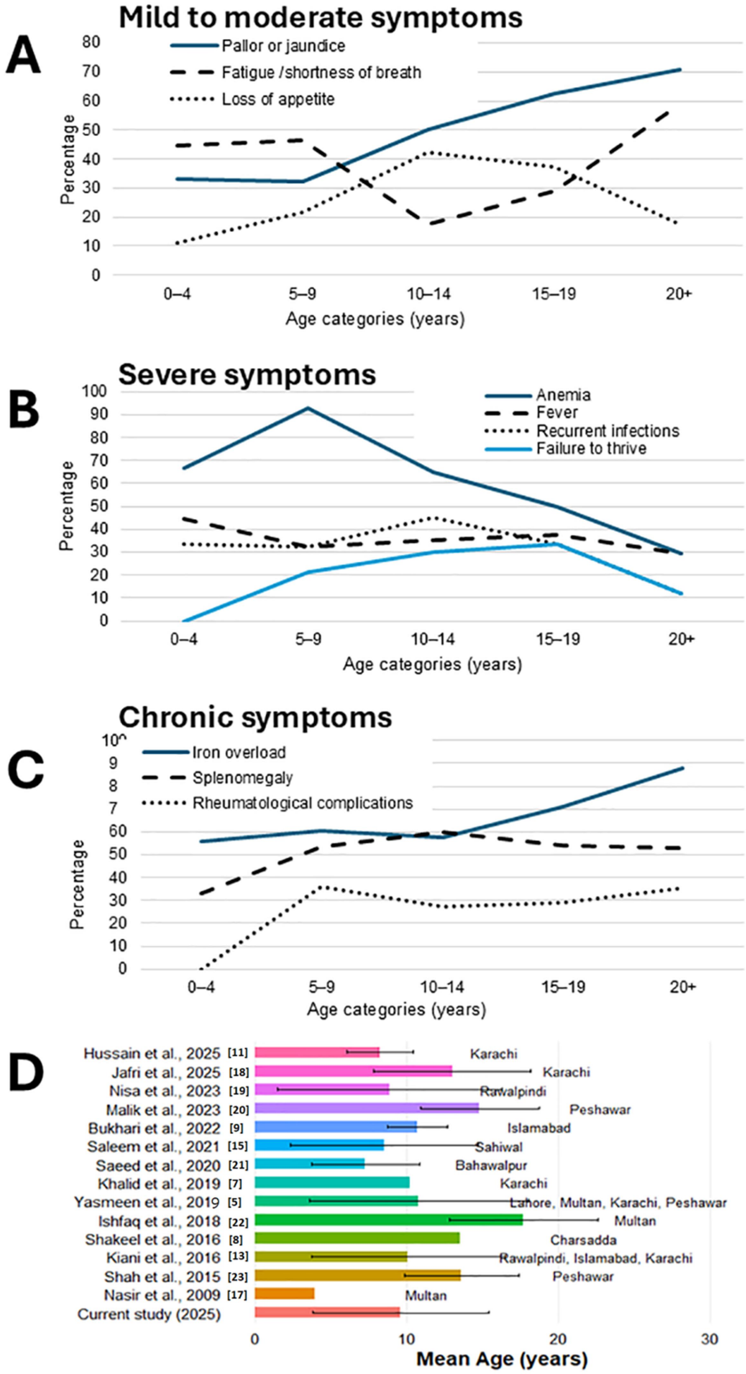
No statistically significant differences were observed across variables; #, odds ratio of affected males against females.

Clinical presentation

The clinical presentation of patients was broadly categorized into three groups:

1. Mild to moderate symptoms – including pallor or jaundice (50%), fatigue or shortness of breath (35%), loss of appetite (31%), vomiting (14%), and diarrhea (13%). The distribution of symptoms across age intervals showed a steady increase in incidence of symptoms (**Figure IA**). These findings indicate that mild clinical symptoms not only persist throughout the lifespan of thalassemia patients but also intensify with age, reflecting progressive disease burden.
2. Severe symptoms – such as anemia (64%), fever (35%), recurrent infections (34%), failure to thrive (24%), and abdominal pain or distention (4%). The distribution of these symptoms across age groups revealed that while anemia is the hallmark of thalassemia, other symptoms like growth failure and infection-related morbidity dominate in childhood and early adolescence (**Figure IB**).
3. Chronic and long-term complications – most commonly iron overload (83%) and splenomegaly (54%), followed by rheumatological complications (29%) and hepatomegaly (14%). The distribution of symptoms across age intervals showed a continuous rise in symptom incidence, suggesting cumulative disease and treatment-related morbidities (**Figure IC**).

Legend to Figure I: Clinical spectrum across age categories of thalassemia patients (n=497). Distribution of mild to moderate symptoms (A), severe (B) and chronic symptoms (C) across age categories. (D) Comparison of mean age (years) of thalassemia patients reported in different studies from Pakistan with the findings of the current study.



Transfusion-related symptoms and familial characteristics of thalassemia patients

The patients had typical transfusion-related symptoms, which are reported in **Table II**.

An estimated 71% of patients had parental consanguinity. In terms of familial/sporadic presentation, 51% of cases were familial, while 49% were sporadic (**Table II**). Among the familial cases, the majority (84%) reported thalassemia affecting only the first generation of the family. Regarding birth order, the first-born (29%) and second-born (23%) were most frequently affected.

A history of thalassemia-related mortality was present in 29% of families, most often involving a single death (73%), followed by two or more deaths (27%).

Overall, the cohort included 911 affected individuals, with a slightly higher proportion of males (500) than females (411). Among families with multiple affected individuals, the majority had two affected members (60%), while 16% had three, 13% had four, and 11% reported five or more affected members.

Table II: Transfusion-related symptoms and familial attributes of thalassemia patients

Variable	Male, No. (%)	Female, No. (%)	Total, No. (%) #
Transfusion frequency (days)			
7–14	10 (18)	7 (19)	17 (18)
15-30	44 (80)	30 (81)	74 (80)
>30	1 (2)	0 (0)	1 (1)
Total	55 (100)	37 (100)	92 (100)
χ^2=0.68; p=0.88			
1st transfusion age (Month)			
≤ 6	30 (55)	19 (53)	49 (54)
6–12	15 (27)	13 (36)	28 (31)
12–24	6 (11)	3 (8)	9 (10)
> 24	4 (7)	1 (3)	5 (5)
χ^2=1.51; p=0.68			
Ferritin level (ranges in ng/ml)			
≤1500	13 (10)	14 (13)	27 (12)
1501–3000	32 (25)	24 (23)	56 (24)
3001–6000	52 (41)	38 (36)	90 (38)
>6000	31 (24)	30 (28)	61 (26)
χ^2=1.32; p=0.73			
Chelation therapy	48 (87)	35 (90)	83 (88)
Hepatitis B/C infection	36 (42)	31 (39)	67 (41)
Parental consanguinity	206 (74)	145 (67)	351 (71)
Familial/sporadic presentation			
Familial	115 (41)	97 (45)	212 (43)
Sporadic	165 (59)	120 (55)	285 (57)
χ^2 0.66; p=0.72			
Disease segregating generations (in familial cases)			
1	121 (85)	90 (83)	211 (84)

2	15 (10)	14 (13)	29 (12)
≥3	7 (5)	4 (4)	11 (4)
$\chi^2=0.21$; $p=0.89$			
History of thalassemia-related mortality (in familial cases)			
Yes	27 (25)	24 (34)	51 (29)
No	79 (75)	47 (66)	126 (71)
$\chi^2=1.44$; $p=0.49$			
No. of mortalities in family (n=51)			
1	21 (78)	16 (67)	37 (73)
≥2	6 (22)	8 (33)	14 (27)
$\chi^2=0.79$; $p=0.67$			
Birth order of the index case			
1st	40 (26)	40 (31)	80 (29)
2nd	43 (28)	20 (16)	63 (23)
3rd	24 (16)	20 (16)	44 (16)
4th	15 (10)	13 (10)	28 (10)
5th and above	28 (19)	14 (11)	42 (15)
$\chi^2=6.56$; $p=0.58$			
Total affected individuals in all families	500 (55)	411 (45)	911 (100)

No statistically significant differences were observed across variables; #, data available.

Caregivers' attitudes towards the causes of mortality in thalassemia patients

The experts' responses supported the patterns observed in our data and revealed consistency with their clinical experiences. They reported that the reduced number of older thalassemia patients is largely attributable to premature mortality rather than treatment non-compliance or under-reporting.

According to the clinicians, suboptimal management and poor adherence to treatment regimens were major contributors to increased complications and early mortality among young patients. They emphasized that inadequate access to quality healthcare services and irregular follow-up further exacerbated these outcomes. Conversely, the experts highlighted that improved healthcare infrastructure, effective therapeutic strategies, and consistent treatment adherence could significantly reduce early mortality and extend life expectancy in patients with beta-thalassemia.

Low life expectancy of thalassemia patients as reported in Pakistani literature

To evaluate the life expectancy of thalassemia patients in Pakistan, a comprehensive review of the national literature was conducted. Relevant studies were screened to extract data on the mean age of patients as well as the highest reported age groups. The compiled results are presented in Figure 1D. The analysis revealed a consistent pattern across studies: the majority of participants were in the pediatric and early adolescent age groups. Reports of patients surviving beyond the age of 20 years were extremely limited, underscoring a markedly low life expectancy within this population.

DISCUSSION

This study provides a comprehensive overview of the demographic, clinical, and transfusion-related characteristics of transfusion-dependent BTM patients from Islamabad/Rawalpindi and the Potohar region, with particular emphasis on age distribution patterns suggesting low life expectancy and early mortality.

Consistent with prior work from other populations in Pakistan, our cohort suggests that the burden of thalassemia falls disproportionately on families from lower socioeconomic strata and rural/peri-urban settings, reflecting structural barriers to prevention, early diagnosis, and comprehensive care.[12] This pattern mirrors national observations that Pakistan lacks a unified, nationwide prevention policy and registry, contributing to a growing pool of transfusion-dependent thalassemia patients and uneven access to safe transfusion and iron-chelation services.

The high consanguinity rate in Pakistan (reported up to 81% in some cohorts) is a key driver of autosomal recessive hemoglobinopathies, including thalassemia[7,12,14]. Concordantly, 71% of the patients in the present cohort had parental consanguinity. Awareness of the link between consanguinity and thalassemia is uneven among Pakistani families[15].

Our analysis underscores that children aged 0–4 years with severe thalassemia frequently experience a cluster of preventable, clinically manageable complications—including recurrent infections or fever, failure to thrive, gastrointestinal disturbances, and hepatosplenomegaly. These early manifestations are strongly linked with increased mortality and lower life expectancy[16]. Their continued occurrence reflects delays in diagnosis, gaps in treatment access, and broader systemic healthcare limitations.

A key finding in our cohort was the markedly low representation of patients beyond the second decade of life (6% aged ≥20 years), suggesting early mortality. This observation echoes findings from other Pakistani settingsx[5,14,17]. The findings were further corroborated by qualitative insights obtained from caregivers during structured interviews, who commonly reported challenges related to limited treatment options, delayed initiation of transfusion regimens, inadequate access to iron chelation therapy, and insufficient specialized care. Collectively, these factors contribute to the early morbidity and mortality observed among thalassemia patients in Pakistan. By contrast, in developed countries, thalassemia patients are increasingly represented across all age groups, reflecting improved long-term survival.[6] In Iran, 20-, 40-, and even 60-year survival rates among β-thalassemia patients reached approximately 85%, 63%, and 54%, respectively[6].

The reasons for low life expectancy in Pakistani thalassemia patients are multifactorial. These can be summarized as follows: irregular and unsafe transfusion access, high iron overload due to limited access to affordable chelation, transfusion-transmitted infections, absence of nationwide genetic counseling programs, and overarching socioeconomic constraintsx[10,11,13]. The convergence of these factors explains the stark contrast between patient survival in Pakistan and high-income countries.

In light of these findings, urgent steps are warranted to improve survival and quality of life in BTM patients. These include expanding access to safe, regular transfusions, subsidizing iron chelation therapy, strengthening blood safety regulations, establishing national screening and genetic counselling programs, and improving early-life supportive care. There should be public education programs on the risks of consanguinity, delivered without stigma and adapted from successful regional models.[2] Without these measures, the current trajectory of early mortality and reduced life expectancy is likely to persist, perpetuating the thalassemia burden in Pakistan.

CONCLUSION

This study highlights the early mortality and low life expectancy among transfusion-dependent β-thalassemia major patients in the twin cities and adjoining regions. The burden of preventable complications, limited access to chelation therapy, a compromised healthcare system and lack of transfusion safety are the principal barriers to improved outcomes. These findings confirm an alarming rate of parental consanguinity, clustering of severe early-life morbidities, and reduced survival beyond the second decade of life. Limited survival into adulthood underscores significant gaps in disease management. Strengthening the existing provincial thalassemia initiatives and expanding them into a coordinated national program are critical to improving survival and reducing the growing thalassemia burden in Pakistan. Future research should prioritize survival assessment and guide a sustainable national thalassemia policy.

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Siddiqui A: Did fieldwork and data collection, performed statistical analysis and manuscript writing, edited, reviewed and approved the manuscript.
Kanhar AA: Did fieldwork and data collection, edited, reviewed and approved the manuscript.
Khan R: Did fieldwork and data collection, edited, reviewed and approved the manuscript.
Muhammad N: Did fieldwork and data collection, edited, reviewed and approved the manuscript.
Naz S: Did fieldwork and data collection, edited, reviewed and approved the manuscript.
Malik M: Conceived, designed and planned the study, edited, reviewed and approved the manuscript.
All authors agree to be accountable for all aspects of the work.

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