Original Article **Open Access**

Depression, Anxiety, and Stress in Beta Thalassemia Patient in Comparison to Siblings

Ahsan Ali Shaikh, Muhammad Ahmad, Khurram Fayyaz, Inshal Jawed, Abu Huraira Bin Gulzar, Saira Zubair

Abstract

Objective: Our study assessed psychological outcomes and health-related quality of life (HRQoL) in transfusion-dependent â-thalassemia patients as compared to their siblings in Pakistan, and identified whether stress and the frequency of transfusions are independent predictors of physical functioning in thalassemia patients.

Study Design and Setting: This analytical cross-sectional survey was conducted at PNS Shifa Hospital, Karachi (January-July 2025).

Methodology: 70 patients aged between 7 and 25 years of confirmed â-thalassemia major, intermedia, or minor were enrolled. Standardized scales have been used: PHQ-9, GAD-7, PSS-10, and SF-12. Mann-Whitney, Kruskal-Wallis, t-tests, and ANOVA were used where appropriate, and a hierarchical linear regression modeled predictor of PCS-12.

Results: The study included 70 patients with transfusion-dependent thalassemia (mean age, 13.4±2.67; 58.6% males), with 78.6% of them having â-thalassemia major. No significant difference was found between the psychological outcomes of the patients as compared to their siblings ($p > 0.05$). The higher the frequency of transfusion, the higher the depression, anxiety, stress, and the lower the mental HRQoL($p<0.05$). In multivariable analyses, stress had an independent relationship to lower PCS-12 (beta=-0.383, $p=0.009$). Perceived stress (beta= -0.511, $p<0.001$) and worse mental HRQoL (beta= -0.433, $p<0.001$) explained 42.7 percent of the variance in PCS-12. When stress was entered alone, it accounted for 27 percent of PCS-12 variance (0.607, $p<0.001$).

Conclusion: Transfusion-related perceived stress appears to be the strongest psychosocial determinant of physical functioning, which undermines mental HRQoL. Moreover, the patients and their families were affected equally. Thus, stress-sensitive care models are required in addition to biomedical monitoring in Pakistan.

Keywords: beta-Thalassemia, Mental Health, Physical Health, Psychological outcomes

How to cite this Article:
Shaikh AA, Ahmad M, Fayyaz K, Jawed I, Gulzar AHB, Zubair S. Depression, Anxiety, and Stress in Beta Thalassemia Patient in Comparison to Siblings. J Bahria Uni Med Dental Coll. 2026;16(1):67-73 DOI: https://doi.org/10.51985/JBUMDC2025688

Ahsan Ali Shaikh *(Corresponding Author)*
Resident, Department of Pediatric Medicine,
PNS SHIFA Hospital, Karachi
Email: ahsan_rkol@hotmail.com

Muhammad Ahmad
Medical Officer, Department of Pediatric Medicine,
PNS SHIFA Hospital, Karachi
Email: drmahmad051@gmail.com

Khurram Fayyaz
Consultant, Department of Pediatric Medicine,
PNS SHIFA Hospital, Karachi
Email: kfc113@hotmail.com

Inshal Jawed
Medical Officer, Department of Pediatric Medicine,
PNS SHIFA Hospital, Karachi
Email: inshaljwd@gmail.com

Abu Huraira Bin Gulzar
Medical Officer, Department of Pediatric Medicine,
PNS SHIFA Hospital, Karachi
Email: abu.huraira.bin.gulzar@gmail.com

Saira Zubair
Resident, Department of Pediatric Medicine,
PNS SHIFA Hospital, Karachi
Email: sairazubair94@gmail.com

Received: 20-08-2025
1st Revision: 04-09-2025
Accepted: 05-01-2026
2nd Revision: 20-10-2025

INTRODUCTION

The β-thalassemia, the set of recessive inherited diseases of globin-chain production, remains a significant global health burden in spite of the progress in transfusion medicine and chelation therapy.[1] According to the World Health Organization (WHO), it is estimated that over 40,000 infants are born with thalassemia annually, with the vast majority of them having β-thalassemia major or intermedia.[2] A recent Global Burden of Disease study demonstrated that, over the past 30 years, the disability-adjusted life-years (DALYs) caused by thalassemia have decreased relatively little compared with other inherited anemias, highlighting the clinical and social burden of extended survival.[2] The geographical distribution of β-thalassemia is clumped around the so-called thalassemia belt, which includes some of the Mediterranean, Middle East, South-East Asia, and Indian subcontinent areas historically under malaria selective pressure. Worldwide, the percentage of carriers is about 1.5, with an estimated 60,000 infants born annually with the disease. So far, more than 350 HBB gene mutations have been reported, of which only twenty mutations contribute to 80 percent of the cases.[3] The burden is not

only in iron overload and endocrine dysfunction, but the need to attend hospitals regularly, treatment exhaustion, and stigma compromise quality of life and exert pressure on already weak health systems, particularly in low-resource countries.[4] Approximately 5-7% of the population, or more than ten million individuals, are carriers of a β-thalassemia mutation, and about 5000-6000 children with transfusion-dependent β-thalassemia are born each year.[3] Unlike the other countries in the neighborhood, which have introduced mandatory premarital screening, prevention programs in Pakistan are patchy and province-specific. Consequently, pediatric and adolescent thalassemia units in large cities are permanently overcrowded, whereas families in rural areas have to travel considerable distances to access safe blood and deferoxamine. Transfusion intervals in publicly funded centers are as low as every two weeks to reach hemoglobin targets, and this imposes repeated direct and indirect costs on households with an average monthly income of less than US$120.[3] There is no established national thalassemia prevention or registry system in Pakistan despite the high carrier rate (57 percent) and the estimated 5,000-6,000 births per year of transfusion-dependent 8-thalassemia. This disjointed landscape has led to NGOs such as the Patients Welfare Association (established in Karachi Civil Hospital) to step in to offer regular transfusions and some chelation services at no cost, albeit to a small group of needy patients.[3] Nonetheless, national guidelines pay almost no attention to psychological screening or social support based on biomedical endpoints of pre-transfusion hemoglobin and serum ferritin.[5]

Psychosocial outcomes-related information is scarce in South Asia. Although literature on Mediterranean and Southeast Asia has associated thalassemia with depression, anxiety, and poor health-related quality of life (HRQoL), cultural issues in Pakistan (such as extended families, consanguineous marriage, and gendered caregiving expectations) reduce its utility. Studies that are available tend to combine children and adults.[6] They infrequently stratify by transfusion burden and rarely measure perceived stress, which has a robust predictive association with physical health. Small qualitative reports from Pakistan suggest that the frequency of hospital visits, rather than genotype or ferritin levels, is the most disruptive factor for families, but these observations remain unquantified.[7] South Asian psychosocial data is limited, but a recent survey revealed that siblings of thalassemia patients develop mild-to-moderate levels of psychological stress, with anxiety and depression being notably common, indicating that the general care model should deal with the health of the family as a whole and not the affected individual.[8]

In this background, we carried out a cross-sectional study in Karachi to compare depression, anxiety, perceived stress, and HRQoL between transfusion-dependent β-thalassemia patients and their siblings. Our hypothesis was that perceived stress, as opposed to conventional disease measures, would best predict physical functioning and that reduced transfusion interval would worsen psychological distress in the patient and their family. In contrast to traditional markers (e.g., hemoglobin, ferritin), perceived stress, as assessed by measures such as the PSS, has been shown to have strong correlations with biological stress, mental health outcomes, and even immune and aging processes, thus supporting its utility as an indicator of physical functioning.[9] We hope to inform family-centered, stress-sensitive models of thalassemia care in Pakistan by producing locally relevant evidence.

METHODOLOGY

This was an analytical cross-sectional survey aimed at evaluating the psychosocial outcomes in β-thalassemia patients. The study was in accordance with the STROBE recommendations on observational studies.[10] The protocol was approved by the Ethical Committee PNS Shifa (ERC/2024/Paeds/133). All procedures conformed to the Declaration of Helsinki.[11] And, the data were de-identified before it left the institution for analysis. We filtered through the registry PNS Shifa and contacted people who matched the eligibility criteria. We aimed at the age group 7 to 25 years, especially encompassing late childhood and early adulthood.

The inclusion criteria were as follows: All of the patients had to be hematologically confirmed beta-thalassemia major, intermedia, or minor according to the lab reports, having a transfusion interval of 12 weeks or less during 12 months or more. Reference range of hemoglobin was set to =9 g/dL -1 at the index visit (to reduce the transient fatigue effects).[12] The patient or their parents must have the capacity to read the Urdu language or English, or to undertake an assisted interview.

Patients were excluded if they had any acute febrile illness, obvious cardiac failure, uncontrolled endocrine disease, or a known congenital or acquired cognitive delay. These conditions could introduce self-reported bias when evaluating the mental-health scores.[12] The data collection was conducted from 12-Jan-2025 to 30-July-2025 at the PNS Shifa Karachi, which is a leading care center for thalassemia patients and serves to provide transfusion and chelation therapies to the patients.

We powered the study to detect a moderate association between perceived stress (PSS-10) and physical HRQoL (SF-12 PCS), specifying ñ = 0.35 a priori. Prior work shows stress–physical HRQoL correlations that are small in healthy student samples (e.g., r ˜ -0.20), but moderate in caregiver and chronic-disease contexts (e.g., r ˜ -0.36 to -0.58), placing 0.35 within the observed mid-range. Sample size (two-sided á = 0.05; power = 0.80) was computed for a correlation test using Fisher's z and verified in GPower 3.1.[13]

A research nurse screened potential participants on the transfusion list of the day. Eligible individuals (and parents of underage individuals) were provided with an information

sheet after phlebotomy and pre-transfusion observations, and written consent (and assent in those under 18 years) was received in a confidential counselling cubicle. Self-administered questionnaires were used; illiterate respondents had their items read aloud word-for-word by the nurses to prevent interpretive bias. The mean completion time was 15 min. Clinical data (genotype and transfusion frequency) were extracted from the electronic record on the same day.

Health-related quality of life (PCS-12, MCS-12) was treated as a continuous variable to quantify overall physical functioning. This was the main endpoint for group comparisons and for regression models examining predictors of physical health. PCS-12 evaluates physical health, specifically physical activity, bodily pain, general health, and role-physical. While MCS-12 focuses on mental health, i.e., vitality, social functioning, role-emotional, and mental health. All of the 12 questions are combined using a published scoring algorithm and yield norm-based scores in the form of mean (SD), where a higher score is better, while scores below 50 reflect worse-than-average health relative to norms. Depression (PHQ-9) analyzed the depression symptoms based on nine questions, each scored between 0 ("not at all") to 3 ("nearly every day"). Finally, scores are summed (0–27). A higher score means more depressive symptoms. According to the conventional bands, 0–4 is regarded as minimal, 5–9 as mild, 10–14 as moderate, 15–19 as moderately severe, and 20–27 as severe. Anxiety (GAD-7) was used to evaluate the anxiety burden using the seven items, each scored 0–3; the total range is 0–21, where higher totals mean greater anxiety. Clinically relevant readings included 5 (mild), 10 (moderate), and 15 (severe). Perceived stress (PSS-10) measured the stress that is evaluated based on how unpredictable or overwhelmed a person feels. It is based on the 10-score items, each ranging from 0-4 ("never" to "very often") with a total score of 0-40. A value of lower than 14 is considered low, between 14 and 26 (moderate), and higher than 27 as high.

All of the analyses were pre-specified and performed as two-sided tests at the level of significance of á =0.05. Continuous data (age; PHQ-9, GAD-7, PSS-10; SF-12 component scores) were described as mean (SD), if they were normally distributed, and as median (IQR) where they were skewed; categorical data (sex, marital status, thalassemia phenotype, transfusion interval categories) were presented as percentages, n (%). The Shapiro-Wilk test, QQ plot, and histograms were used to analyze the distribution of the data. For normal data, parametric tests were utilized (independent-samples t or one-way ANOVA) while for skewed or non-normal data, non-parametric tests (Mann-Whitney U or Kruskal-Wallis or Chi-square) were employed accordingly.

We used hierarchical linear regression to model PCS-12 (continuous) as a predictor of physical functioning to determine independent predictors of physical functioning. Predictors were added in conceptually sequential blocks: Block 1, demographics; age (years), and sex (M/F); Block 2, clinical load; thalassemia phenotype (dummy-coded with beta-thalassemia minor as reference), and transfusion interval (coded by weekly intervals); Block 3, psychological variables; PHQ-9, GAD-7, PSS-10, and MCS-12. Standardization of psychological predictors was done to bring the coefficients to a similar scale. Assumptions of the models (linearity, normality of the residuals, homoscedasticity, and multicollinearity) were thoroughly tested and found acceptable. We present standardized β coefficients, 95% CIs, p-values, and model fit (adjusted R^2). Data management, assumption diagnostics, and analysis were all carried out in IBM SPSS Statistics, version 25 (IBM Corp.).

RESULTS

Seventy transfusion-dependent β-thalassemia patients (age 7–25 y; mean 13.4 ± 2.67) and 40 accompanying siblings (mean age 15.5 ± 4.3 y) were enrolled. Males accounted for 58.6% of patients and 53.5% of siblings. Most patients had β-thalassemia major (78.6%), while siblings were unaffected. Nearly all participants in both groups were unmarried. Patients most often received transfusions every four weeks (52.2%), with intervals ranging from two to twelve weeks. Baseline sociodemographic characteristics were broadly comparable between patients and siblings [Table 1, 2].

Depression, anxiety, and stress scores were low to moderate across both groups. Among patients, mean PHQ-9 was 3.37 ± 3.47, GAD-7 was 3.58 ± 3.01, and PSS-10 was 13.91 ± 4.74. Siblings showed a similar pattern: 86.1% reported minimal depressive symptoms, 74.4% minimal anxiety, and 67.4% moderate stress. Comparison testing (Fisher's Exact) showed no statistically significant differences between

Table 01: Demographic characteristics of the â-Thalassemia patients

Demographics	â-Thalassemia Patients N (%)	Siblings N (%)
Gender		
Female	29 (41.4)	20 (46.5)
Male	41 (58.6)	23 (53.5)
Age, mean (SD)	13.4 (2.67)	15.5 (4.3)
Marital status		
Married	4 (6)	5 (11.6)
Single	66 (94)	38 (88.4)
Type of Thalassemia		
B Thalassemia Minor	5 (7.1)	-
B Thalassemia Intermediate	10 (14.3)	-
B Thalassemia Major	55 (78.6)	-
Frequency of Transfusions		
Every 2 weeks	6 (8.7)	-
Every 3 weeks	9 (13)	-
Every 4 weeks	36 (52.2)	-
Every 5 weeks	17 (24.6)	-
Every 12 weeks	1 (1.4)	-

Table 03: Mann-Whitney U test was used to evaluate the relation between Gender, age, and psychological state (PHQ-9, GAD-7, PSS scores, MCS-12, PCS-12). While the Kruskal-Wallis test was used to find the association of age, gender, psychological state with the Type of â-Thalassemia and frequency of transfusions. The table shows the reported p-values

Categories	Age	PHQ-9	GAD-7	PSS	MCS 12	PCS-12
Gender	0.211	0.559	0.758	0.943	0.95	0.335
Type of β-Thalassemia	0.968	**0.034***	0.211	**0.013***	0.875	0.928
Frequency of Transfusions	0.463	**0.041***	**0.025***	**0.008***	**0.007***	0.757

Student t test was used to evaluate the difference of means for gender in PCS-12

One way ANOVA was used to evaluate the difference of means based on thalassemia type and number of transfusions

* P-value is significant ($\alpha = 0.05$)

Table 02. Comparison of Psychological Outcomes in â-Thalassemia Patients vs. Siblings

Categories	â-Thalassemia Patients N (%)	Siblings N (%)	p-value
Stress (PSS-10)			
Low stress	25 (35.7)	14 (32.6)	0.31*
Moderate stress	41 (58.6)	29 (67.4)	
Anxiety (GAD-7)			
Minimal anxiety	47 (67.1)	32 (74.4)	0.43*
Mild anxiety	16 (22.9)	7 (16.3)	
Moderate anxiety	4 (5.7)	4 (9.3)	
Depression (PHQ-9)			
Minimal depression	57 (81.4)	37 (86.1)	0.86*
Mild depression	8 (11.4)	4 (9.3)	
Moderate depression	4 (5.7)	1 (2.3)	
Moderately severe depression	1 (1.4)	1 (2.3)	

*****Fisher's Exact Test was used to evaluate any difference between the two groups

Table 04: Multiple linear regression models predicting PCS-12 based on the predictors: Gender, Type of thalassemia, Number of Transfusions, Depression, Anxiety, Stress, and MCS-12 scores

Model 1 (Adjusted R-squared= .07)	â-coefficient	P-value
Gender	0.02	0.908
Type of â-Thalassemia	-0.13	0.374
Number of Transfusions	-0.11	0.488
Depression	-0.12	0.458
Anxiety	0.06	0.724
Stress	-0.38	**0.009***
Model 2 (Adjusted R-squared= .43)		
PHQ-9 scores	-0.02	0.871
GAD-7 scores	-0.1	0.448
PSS score	-0.51	**<0.001***
MCS-12	-0.43	**<0.001***
Model 3 (Adjusted R-squared= 0.27)		
PHQ-9 score	0.07	0.619
GAD-7 scores	0.05	0.743
PSS score	-0.61	**<0.001***

patients and siblings across depression, anxiety, stress, or HRQoL domains (all $p > 0.05$) [Table 2]. This indicates that the psychosocial burden extends beyond patients to their siblings.

No significant sex differences were observed among patients in depression, anxiety, stress, PCS-12, or MCS-12 (all $p > 0.05$). Across thalassemia major, intermedia, and minor, depressive symptoms ($p = 0.034$) and perceived stress ($p = 0.013$) differed modestly, but no significant group differences were seen for anxiety, PCS-12, or MCS-12. This suggests that while clinical phenotype influences distress modestly, the overall psychosocial profile of patients still mirrors that of their siblings. Among patients, shorter transfusion intervals were associated with higher depression ($p = 0.041$), anxiety ($p = 0.025$), stress ($p = 0.008$), and lower mental HRQoL ($p = 0.007$). PCS-12 did not differ significantly ($p = 0.757$). These findings reinforce that the psychosocial burden in patients arises more from treatment intensity than from disease biology alone. [Table 3]

Regression modeling showed that stress was the only independent predictor of poorer PCS-12 in patients ($\beta = –0.383$, $p = 0.009$). When psychological variables were entered together, perceived stress ($\beta = –0.511$, $p < 0.001$) and lower MCS-12 ($\beta = –0.433$, $p < 0.001$) explained 42.7% of the variance. Importantly, this aligns with the comparative findings: although siblings were clinically unaffected, they reported similar stress levels, highlighting stress as a shared determinant of functioning within thalassemia families [Table 4].

DISCUSSION

Our study found no difference between the psychological outcomes of the patients and their siblings. This lies in parallel to the results of Ajij M et al. 2015. They reported that thalassemia patients and their siblings scored significantly lower in the environment when compared to the control.[14] Similarly, another study highlighted that patients with transfusion-dependent thalassemia go through significant mental burden as well as economic stress. They stressed the

need for improved HRQoL care in order to have better outcomes and reduce the emotional stress bear by this group.[15] Similarly, Lodhi et al. conducted a 2025 cross-sectional study in Bhopal. They included 95 siblings of multi-transfused Thalassemia Patients aged 2 to 18, and found that more than half reported moderate perceived stress on the PSS-C, whereas low stress in the rest. Most importantly, internalizing symptoms (e.g., anxiety, depression) were positive in at least one third of them, with smaller percentages indicating attention and externalizing issues. Moreover, advanced age was a predictor of increased likelihood of internalizing pathology. Therefore, we can conclude that the siblings of transfusion-dependent thalassemia patients are not just passive observers but demonstrate measurable stress and internalizing symptoms and should be considered a vulnerable population that needs family-centered psychosocial interventions.[8]

Our study observed that both transfusion-dependent patients and their siblings had moderate stress with minimal depression and anxiety. It was consistent with the literature on chronic illnesses. As Pawlowski et al. found, people with long-term conditions experienced a higher perceived stress regardless of official psychiatric diagnosis, placing stress as a marker of perceived burden unrelated to disease.[16] In the thalassemia context, this is reflective of the constant anxiety over the availability of safe blood, the pain of accessing a vein, and hospital logistics, which are felt by both patients and their siblings visiting the care facilities. Smith et al. further emphasized the situation by reporting that the caregivers of chronically ill children never take a sigh of relief, and the anticipatory vigilance that the Pakistani siblings experience by missing school, witnessing repetitive blood transfusions, and internalizing the worsening socioeconomic remuneration of the family.[17] The concept analysis put forth by Davis elucidated stress as overload, unpredictability, and loss in coping confidence, exactly the factors that prevail in the lives of transfusion-dependent families, where uncertainties of monthly transfusions and financial toxicity dominate everyday household life.[18] Therefore, the stress scales can measure total allostatic load of the family, and the syndromal batteries are simply under-sensitive in such a cultural and developmental environment. We can infer then that the management of thalassemia cannot be patient-centered; there is the psychosocial imprint of stress on the siblings that can only be addressed with the transition to being family-centered in thalassemia transfusion programs.

Our findings indicate that shorter transfusion intervals had a consistent adverse impact on all depression, anxiety, and stress measures and MCS-12, although physical functioning (PCS-12) was largely unaffected. This implies that among those who undergo frequent transfusions, a psychosocial trace is more likely to be attributed to the logistic disturbances than to somatic deterioration. Sobota et al. (2011) found comparable results in the Thalassemia Longitudinal Cohort of adolescents and adults with transfusion-dependent thalassemia who had a considerably lower score in SF-36 mental domains than U.S. norms, with the degree of treatment intensity serving as an important predictor of impairment.[19] Among our cohort, the same pattern was found: the greater the number of transfusions per month, the clearer a decline of mental well-being was, even without any significant changes in the physical health status.

Transfusion days required an almost ten-hour investment of patients' and caregivers' time, with associated patient and caregiver fatigue, anticipatory anxiety, and caregiver strain. Notably, these destabilizations affect siblings as well, who have to miss school, wait long hours at hospitals, and bear the costs involved and the emotional burden of frequent visits. The association between frequency of transfusion, economic burden, and deterioration of HRQoL in Bangladeshi patients further confirmed our interpretation that psychosocial stress is enhanced by treatment burden in South Asia, a resource-limited region.[20] Collectively, these results position the frequency of transfusion as both a biomedical imperative and a stress-amplifier at the family level. The anticipation, pain, and disruption fuel moderate stress (but not much in the way of syndromal anxiety or depression) in patients. To siblings, this similar exposure to the disruptors means the same feelings of stress, balancing the anticipated patient-sibling disparity. Therefore, although transfusions continue to be life-saving, the psychosocial opportunity cost is high, and there is a need to intervene at a systems level, either through longer transfusion intervals, day-care models, which disrupt less, or family-centered psychosocial interventions at transfusion units.

Depressive symptoms and perceived stress were significantly less distinct in our cohort; in-between β-thalassemia phenotypes, however, there were no significant differences in PCS-12 or MCS-12. This is in agreement with Scalone et al. (2008), who observed that health-related quality of life was inferior in all phenotypes, and differences were minimized after adjusting for transfusion modality and chelation adherence.[21] Genotype, although clinically important in the administration of transfusions and iron collection risks, does not seem to be a useful surrogate measure of psychosocial burden. Despite reduced morbidity overall, β-thalassemia intermedia, due to less-routine transfusions, has a different multi-organ comorbidity burden-imposed by relative iron overload and hypercoagulability-with high rates of extramedullary hematopoiesis, skeletal deformity, and diffuse spleno-/ hepatomegaly; these long-term and unpredictable morbidities have a significant psychosocial burden.[22] In agreement with this, adults with transfusion-independent β-thalassemia intermedia report lower HRQoL than regularly transfused thalassemia major (TM), a fact that has been ascribed to shorter time since diagnosis and a higher multiplicity of complications - an

effect that may reflect on the uncertainty of care as being more disruptive than the intensity of regimented care.[23]

Our data indicate that the psychological outcomes are influenced more by the environment in which the family lives with the transfusion-dependent child than by genotype. This finding aligns with those of regional studies, including Ansari et al. (2014) in Iran, which identified that access to care and adherence to chelation and socioeconomic issues predicted mental-health outcomes much more than phenotype.[24] The findings that large genotype-specific differences in psychosocial scales are absent indicate that this is not a measurement factor but rather emphasize the involvement of the system-level stressors to which all phenotypes are exposed. In relation to policy and clinical pathway, it means that to carry out psychosocial screening should be uniform across all phenotypes of thalassemia (and not concentrated on major disease) as the patients and their siblings possess similar stress levels regardless of genotype.

In our study, we did not find any significant association between males and females in terms of depression, anxiety, stress, or HRQoL scores. This is consistent with the previous literature indicating that the gender impact in thalassemia is irregular and frequently weakened when clinical components are adjusted. A study by Sobota et al. (2011) found that the overall HRQoL among females in the Thalassemia Longitudinal Cohort is lower than in males, and those differences become insignificant after controlling for the severity of the disease itself.[19] Consistent with the findings of Scalone et al. (2008), gender was not an independent predictor of quality of life among Italian patients after considering the effects of chelation adherence and complications.[21] Ansari et al. (2014) also demonstrated no significant between-gender disparities in psychosocial measures in a regional cohort of Iran.[24] Collectively, these results indicate that the prevailing factors determining psychosocial outcomes in transfusion-dependent thalassemia are treatment intensity and clinical burden, and not biological sex.

Lastly, our sample showed low depression and anxiety scores with moderate stress. As reported earlier, in thalassemia, symptoms may be aggravated with time, possibly as a result of accumulated complications, changing social roles, and chelation fatigue, thus showing a clustering effect over time.[25] In this respect, every individual passes through a pre-transition period whereby the structured support from family, colleagues, and transfusion facility staff can help buffer the stress and cope with it better during regular transfusions. Longitudinal follow-up during the years of transition can also be significant to elucidate the paths and prevention windows. Frequent transfusions elevate perceived stress and erode mental HRQoL; stress, in turn, is the proximate predictor of diminished physical functioning. Genotype and sex are secondary once treatment intensity and service exposure are in view.

Psychosocial needs are yet to be addressed in the low-resource transfusion centers in Pakistan. Our results indicate that it is the measure of stress, not the measure of depression or anxiety, that best predicts functioning and that siblings do share this invisible load. Short stress screening could be incorporated at transfusion visits, low-cost counseling could be provided, and family-centered support models could be created, which can help in reducing this disruption. Multicentric, longitudinal studies in the future are needed in order to inform scalable, culturally sensitive interventions in a wide variety of Pakistani contexts.

Our study has several limitations. One, it had a cross-sectional design and measured the quality of life at one point in time. And patients came from one public day-care center, so the results may not be generalizable across Pakistan. Second, the sample size was limited, and some subgroups were small (e.g., β-Thalassemia intermedia, and minor). This limits power for detecting subtle differences by sex or genotype, and it widens confidence intervals. Third, our reliance on self-reported scales (PHQ-9, GAD-7, PSS-10, SF-12) introduces bias as these scales are only screening tools and do not make clinical diagnoses. Our study could not account for several confounding factors, like annual transfusion volume, pre-transfusion haemoglobin, serum ferritin level trends, chelation type, adherence/compliance of patients, endocrine complications, splenectomy status, pain scores, sleep quality, or family income. Fourth, our study also had selection bias. We enrolled patients based on convenience sampling, i.e., those who attended the day-care unit and were well enough to complete questionnaires. Moreover, our regression treated effects as additive and linear; we did not test interactions (e.g., stress × transfusion interval), so more complex relationships might be missed. Finally, we could not include qualitative interviews. Numbers tell us that stress matters; they do not tell us which parts of the care journey are most stressful.

CONCLUSION:

Our paper reports that Transfusion Dependent β-thalassemia patients show no difference in psychosocial burden in comparison with their siblings, with perceived stress as the key indicator of strength in physical functioning and HRQoL. Contrary to the depression or anxiety scores, which were much lower when measured in stress, the scores were high enough, and they alone significantly worsened the physical health. The frequency of transfusion added to this burden, highlighting how treatment logistics and not genotype or sex have the most significant impact on mental well-being. These results recontextualize the task of thalassemia care as an issue of an individual on a family scale, with disclosure of siblings as a vulnerable, yet frequently ignored, category. To achieve this, it is critical to integrate stress-sensitive screening and psychosocial support into transfusion programs to go beyond survival, to dignified survivorship in a low-resource setting.

Conflicts of interest: Nil

Source of Funding: Nil

Acknowledgement: Nil

Authors Contribution:
Ahsan Ali Shaikh: Conception, Design, Analysis and Interpretation of data
Muhammad Ahmad: Conception, Design, Analysis and Interpretation of data
Khurram Fayyaz: Conception, Design, Analysis and Interpretation of data
Inshal Jawed: Conception, Manuscript Writing and Interpretation of data
Abu Huraira Bin Gulzar: Manuscript Writing and Interpretation of data
Saira Zubair: Manuscript Writing and Interpretation of data

REFERENCES:

1. Njeim R, Naouss B, Bou-Fakhredin R, Haddad A, Taher A. Unmet needs in â-thalassemia and the evolving treatment landscape. Transfus Clin Biol. 2024;31(1):48-55. https://doi.org/10.1016/j.tracli.2023.12.003
2. Forni GL, Grazzini G, Boudreaux J, Agostini V, Omert L. Global burden and unmet needs in the treatment of transfusion-dependent â-thalassemia. Frontiers in Hematology. 2023;Volume 2 - 2023. https://doi.org/10.3389/ frhem.2023.1187681
3. Khaliq S. Thalassemia in Pakistan. Hemoglobin. 2022;46(1):12-4. https://doi.org/10.1080/03630269.2022.2059670
4. Tuo Y, Li Y, Li Y, Ma J, Yang X, Wu S, et al. Global, regional, and national burden of thalassemia, 1990-2021: a systematic analysis for the global burden of disease study 2021. EClinicalMedicine. 2024;72:102619. DOI: 10.1016/j.eclinm.2024.102619
5. Saif S, Lila S, Ghani G, Rahat MA, Rasool A, Israr M. Clinical Insights: Prevalence of â-Thalassemia Mutations (IVSI-5, FSC8/9, and CD41/42) in the Swat District. Journal of Bio-X Research. 2024;7:0004. DOI: 10.34133/jbioxresearch.0004
6. Wangi K, Birriel B, Smith C. Psychosocial burden in transfusion dependent beta-thalassemia patients and its impact on the quality of life and the problem of dignity. J Taibah Univ Med Sci. 2023;18(6):1217-9. doi: 10.1016/j.jtumed.2023.05.002
7. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9. DOI: 10.1016/S0140-6736(07)61602-X External Link
8. Lodhi P, Sharma S, Singh P, Agrawal A. Psychosocial Problems in the Siblings of Multitransfused Thalassemia Patients. Cureus. 2025;17(6):e86443. DOI: 10.7759/cureus.86443
9. Knight EL, Jiang Y, Rodriguez-Stanley J, Almeida DM, Engeland CG, Zilioli S. Perceived stress is linked to heightened biomarkers of inflammation via diurnal cortisol in a national sample of adults. Brain Behav Immun. 2021;93:206-13. https://doi.org/10.1016/j.bbi.2021.01.015
10. Cuschieri S. The STROBE guidelines. Saudi J Anaesth. 2019;13(Suppl 1):S31-s4. DOI: 10.4103/sja.SJA_543_18
11. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4. doi:10.1001/jama.2013.281053
12. Ababneh S, Siyam AAA, Alzoubi MM, Al-Sawalha NA, Al Sukhni FF, Al Rahbeni T, et al. Assessment of health-related quality of life in transfusion dependent beta thalassemia. Scientific Reports. 2025;15(1):32267.
13. Carpi M, Milanese A, Cattaruzza MS, Ferrara C, Liuccio M, Vestri A. Well-being, Perceived Stress and Their Relations with Health-Relevant Behaviours Among Italian Medical Students: a Cross-Sectional Study at Sapienza University of Rome. Trends in Psychology. 2022;30(3):425-41. https://doi.org/10.1007/s43076-021-00114-x
14. Ajij M, Pemde HK, Chandra J. Quality of Life of Adolescents With Transfusion-dependent Thalassemia and Their Siblings: A Cross-sectional Study. J Pediatr Hematol Oncol. 2015;37(3):200-3. DOI: 10.1097/MPH.0000000000000244
15. Drahos J, Boateng-Kuffour A, Calvert M, Levine L, Dongha N, Li N, et al. Health-related quality of life and economic impacts in adults with transfusion-dependent â-thalassemia: findings from a prospective longitudinal real-world study. Qual Life Res. 2025;34(7):2005-17. https://doi.org/10.1007/s11136-025-03961-8
16. Paw³owski M, Fila-Witecka K, £uc M, Senczyszyn A, Rymaszewska J, Paw³owska E, et al. Perceived stress level among patients with chronic illness during covid pandemia. Eur Psychiatry. 2021;64(Suppl 1):S286-7. doi:10.1192/j.eurpsy.2021.768
17. Smith S, Tallon M, Clark C, Jones L, Mörelius E. "You Never Exhale Fully Because You're Not Sure What's NEXT": Parents' Experiences of Stress Caring for Children With Chronic Conditions. Frontiers in Pediatrics. 2022;Volume 10 - 2022. https://doi.org/10.3389/fped.2022.902655
18. Davis SL, Soistmann HC. Child's perceived stress: A concept analysis. J Pediatr Nurs. 2022;67:15-26. https://doi.org/10.1016/j.pedn.2022.07.013
19. Sobota A, Yamashita R, Xu Y, Trachtenberg F, Kohlbry P, Kleinert DA, et al. Quality of life in thalassemia: a comparison of SF-36 results from the thalassemia longitudinal cohort to reported literature and the US norms. Am J Hematol. 2011;86(1):92-5. doi: 10.1002/ajh.21896
20. Hossain MJ, Islam MW, Munni UR, Gulshan R, Mukta SA, Miah MS, et al. Health-related quality of life among thalassemia patients in Bangladesh using the SF-36 questionnaire. Sci Rep. 2023;13(1):7734. https://doi.org/10.1038/s41598-023-34205-9
21. Scalone L, Mantovani LG, Krol M, Rofail D, Ravera S, Bisconte MG, et al. Costs, quality of life, treatment satisfaction and compliance in patients with beta-thalassemia major undergoing iron chelation therapy: the ITHACA study. Curr Med Res Opin. 2008;24(7):1905-17.
22. Musallam KM, Taher AT, Rachmilewitz EA. â-thalassemia intermedia: a clinical perspective. Cold Spring Harb Perspect Med. 2012;2(7):a013482. doi: 10.1101/cshperspect.a013482
23. Musallam KM, Khoury B, Abi-Habib R, Bazzi L, Succar J, Halawi R, et al. Health-related quality of life in adults with transfusion-independent thalassaemia intermedia compared to regularly transfused thalassaemia major: new insights. Eur J Haematol. 2011;87(1):73-9.
24. Ansari S, Baghersalimi A, Azarkeivan A, Nojomi M, Hassanzadeh Rad A. Quality of life in patients with thalassemia major. Iran J Ped Hematol Oncol. 2014;4(2):57-63.
25. Mednick L, Yu S, Trachtenberg F, Xu Y, Kleinert DA, Giardina PJ, et al. Symptoms of depression and anxiety in patients with thalassemia: prevalence and correlates in the thalassemia longitudinal cohort. Am J Hematol. 2010;85(10):802-5. https://doi.org/10.1002/ajh.21826