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Psychosocial and Functional Burden in Transfusion-Dependent Hemoglobinopathies: Clinical and Transfusion-Related Correlates in an Albanian Observational Cohort

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Abstract: ***Background: Regular transfusion improves survival in transfusion-dependent hemoglobinopathies, but chronic disease and treatment may affect daily functioning and psychosocial well-being. Aim: To describe patient-reported psychosocial and functional burden and examine its clinical and transfusion-related correlates. Materials and Methods: This cross-sectional observational study included 115 patients aged over 15 years receiving regular transfusions and followed during 2025 at a specialized hemoglobinopathy center in Albania. A researcher-developed questionnaire assessed seven psychosocial and functional domains. Correlation and logistic regression analyses examined associations with clinical and transfusion-related characteristics. Results: Fatigue affected daily activities in 83.5% of participants, 93.0% reported an effect on educational performance, 97.4% did not participate in sports, and 93.9% reported having experienced hopelessness. Higher pretransfusion hemoglobin and longer transfusion intervals were associated with lower odds of several adverse outcomes, whereas older age and severe iron overload were associated with greater burden in selected domains. Conclusion: Patients with transfusion-dependent hemoglobinopathies experience substantial psychosocial and functional burden despite the clinical benefits of transfusion therapy. Patient-reported assessment and multidisciplinary psychological, educational, social, and vocational support should complement routine clinical monitoring.***

Keywords: Hemoglobinopathies, Blood transfusion, Quality of life, Daily functioning, Psychosocial burden, Fatigue, Patient-reported outcomes

1. Introduction

Hemoglobinopathies- particularly transfusion-dependent thalassemia and sickle cell disease- have evolved from disorders associated with significant childhood morbidity and mortality into chronic conditions requiring lifelong multidisciplinary management [1]. Advances in transfusion therapy, iron chelation, and comprehensive care have significantly improved survival and clinical outcomes. However, regular transfusion therapy demands frequent hospital visits, continuous medical monitoring, a treatment-related burden, and the need to adapt to a lifelong chronic illness [1, 2].

In daily clinical practice, the burden of this long-term treatment is evident not only in hematological parameters but also in patients' attitudes toward repeated hospital visits and their concerns regarding education, employment, social participation, and future independence. Patients may present for transfusions exhibiting emotional distress or fatigue, while simultaneously recognizing the treatment's vital role in maintaining their health. This coexistence of clinical benefit and treatment burden underscores the importance of evaluating outcomes that extend beyond hemoglobin levels and disease control.

Health-related quality of life (HRQoL) has consequently become an important patient-reported outcome for individuals with hemoglobinopathies. Chronic anemia, pain, disease-related complications, treatment requirements, and psychosocial stressors can negatively affect physical, emotional, and social functioning. A comprehensive systematic review of 102 studies showed that HRQoL assessment in hemoglobinopathies increasingly incorporates both generic instruments- such as the SF-36 and PedsQL- and disease-specific instruments, including TranQol for transfusion-dependent thalassemia [3].

In transfusion-dependent thalassemia, limitations may extend to education, employment, social integration, and psychological well-being. The 2025 Thalassaemia International Federation guidelines emphasize that quality of life should be considered an integral component of comprehensive care and recommend patient-reported outcome measures to better understand the burden of disease and treatment. They also highlight the importance of supporting social integration and enabling patients to maintain education and employment alongside transfusion care [4].

Several validated instruments can be used to measure health-related quality of life (HRQoL). TranQol was designed to assess quality of life in patients with transfusion-dependent thalassemia. The tool covers several domains, including physical, emotional, family relationships, and school-career functioning. Its validity and reliability have been demonstrated in different populations, including a Greek validation study [5]. However, specific instruments may not always capture patients' broader concerns and whether the target population is adequately represented by the instrument

in a given social, cultural, or healthcare context. Moreover, health-related quality of life and patients' experience are two different concepts; the former refers to how people evaluate their health status, and the latter emphasizes the perspective of patients on healthcare encounters and treatment burden [6].

In Albania, where patients with transfusion-dependent hemoglobinopathies require long-term regular hospital-based care, there is limited published evidence describing how this treatment affects everyday life from the patients' perspective. Therefore, the present study aimed to describe the patient-reported impact of chronic hemoglobinopathy and regular blood transfusion on daily life using a researcher-developed questionnaire. The questionnaire explored fatigue, emotional well-being, social life, educational and occupational functioning, self-perception, and future perspectives among patients regularly followed at a specialized hemoglobinopathy center in Albania. By identifying areas of psychosocial and functional burden, the study seeks to support the development of multidisciplinary interventions aimed not only at prolonging survival but also at improving patients' ability to participate fully in everyday life.

2. Materials and methods

2.1 Study design and setting

This observational cross-sectional study was performed at the Hemoglobinopathy Center of the University Hospital Center "Mother Teresa," Tirana, Albania. Patients with chronic hemoglobinopathy who require regular blood transfusion therapy were enrolled during their follow-up at the institution in 2025. The objectives of the study were to assess the self-perceived impact of chronic hemoglobinopathy and regular blood transfusion therapy on their daily functioning, psychological state, educational and work performance, and future perspectives. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for observational studies.

2.2 Study population

A total of 115 patients aged >15 years with transfusion-dependent hemoglobinopathies were included. The selected patients were those who had an established diagnosis of a chronic hemoglobinopathy, were receiving regular red blood cell transfusions, were actively followed at the Hemoglobinopathy Center during 2025, and were able to understand and complete the questionnaire.

2.3 Data collection

Demographic and clinical information was obtained from medical records and routine clinical follow-up. Variables included age, sex, underlying hemoglobinopathy, duration of transfusion therapy, transfusion frequency, and relevant treatment-related characteristics available in the medical records.

Patient-reported information was collected using a researcher-developed questionnaire specifically designed for this study. The questionnaire was developed to explore aspects of patients' everyday experiences that may not be fully represented by routine hematological parameters or generic clinical assessments.

The questionnaire focused on several predefined domains:

1) Physical and functional well-being, including fatigue and limitations in daily activities;
2) Emotional well-being, including emotional responses to chronic disease and long-term treatment;
3) Social functioning, including participation in social activities and relationships;
4) Educational functioning, including school/university attendance and perceived effects on academic performance;
5) Occupational functioning, including perceived limitations in employment and professional activities;
6) Self-perception and self-esteem, including perceptions of physical appearance and personal capabilities; and
7) Future perspectives, including expectations, ambitions, and perceptions regarding education, employment, social life, and independence.

The questionnaire was administered directly to participants, and responses were recorded anonymously. Participants were encouraged to provide responses based on their own experiences during the preceding period of regular treatment and follow-up.

2.4 Researcher-developed questionnaire

The questionnaire was designed by the researchers based on the clinical practice of the Hemoglobinopathy Center, the relevant literature data on the psychosocial burden associated with hemoglobinopathies, and the key domains identified as critical for long-term transfusion therapy. As the questionnaire was created for the specific purpose of this study, it was not validated in advance, and the results were interpreted as patient-reported outcomes, addressing their impact on function and related domains, rather than as a validated measure of HRQoL. Wherever applicable, the items were organized in sets of response options that could be evaluated quantitatively. The responses were coded by numbers for statistical analyses. The questionnaire was administered in Albanian language, understandable to the participants, using precise and relevant wording.

2.5 Outcomes

The primary outcome of the study was the psychosocial and functional burden associated with transfusion-dependent hemoglobinopathies, assessed using a researcher-developed questionnaire. The questionnaire evaluated seven domains: fatigue, daily activity impairment, educational difficulties, social restriction, appearance satisfaction, hopelessness, and future enthusiasm.

For the regression analyses, each questionnaire domain was analyzed as a binary outcome, according to the predefined response categories of the questionnaire. Responses indicating the presence of the respective psychosocial or functional problem were coded as 1, while responses indicating its absence were coded as 0. Thus, separate binary logistic regression models were constructed for each domain.

The principal clinical and treatment-related explanatory variables were age, diagnosis, serum ferritin concentration, transfusion interval, and pretransfusion hemoglobin (Hb). Age was analyzed as a continuous variable and expressed per 10-year increase. Serum ferritin was additionally categorized according to the clinically relevant threshold of >2500 ng/mL, representing severe iron overload, versus ≤2500 ng/mL. Transfusion interval was expressed per 2-week increase, while pretransfusion Hb was expressed per 1 g/dL increase.

The secondary outcomes were the individual questionnaire domains and their associations with clinical and transfusion-related characteristics.

The study did not interpret individual questionnaire responses as clinical diagnoses of depression, anxiety, or other psychiatric disorders.

2.6 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized using the mean ± standard deviation (SD) for approximately normally distributed variables or the median and interquartile range (IQR) for non-normally distributed variables. Categorical variables were presented as absolute frequencies and percentages.

Associations between clinical and transfusion-related variables and the questionnaire domains were initially evaluated using Spearman's rank correlation coefficient (r_s) for continuous or ordinal questionnaire measures, as appropriate. Correlation coefficients were reported together with two-sided p-values. To account for multiple testing across the 35 correlation analyses, false discovery rate (FDR) adjustment using the Benjamini–Hochberg procedure was applied, with an adjusted p-value <0.05 considered statistically significant.

For the principal binary outcomes, univariable binary logistic regression was performed to evaluate the association between individual clinical or transfusion-related variables and each psychosocial/functional outcome. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and p-values were reported.

Variables considered clinically relevant and/or showing evidence of association in univariable analyses were entered into multivariable binary logistic regression models. The principal multivariable models included age, diagnosis, ferritin category (>2500 vs ≤2500 ng/mL), transfusion interval, and pretransfusion Hb. Age was expressed per 10-year increase, transfusion interval per 2-week increase, and pretransfusion Hb per 1 g/dL increase. For categorical variables, clinically appropriate reference categories were specified, with SCD used as the reference category for diagnosis and ferritin ≤2500 ng/mL as the reference category for ferritin.

Adjusted odds ratios (aORs), 95% CIs, and p-values were reported for the multivariable models. An OR >1 indicated higher odds of the respective adverse psychosocial or functional outcome, whereas an OR <1 indicated lower odds.

Because the study was observational and cross-sectional in nature, associations were interpreted as statistical associations rather than causal effects.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant unless otherwise specified for multiple-comparison-adjusted analyses.

3. Results

3.1 Demographic and clinical characteristics of the study population

A total of 115 patients with transfusion-dependent hemoglobinopathies were included in the questionnaire-based study. The study population included 59 males (51.3%) and 56 females (48.7%). Regarding age distribution, 14 participants (12.2%) were younger than 18 years, 57 (49.6%) were aged 18–30 years, and 44 (38.3%) were older than 30 years. β-Thalassemia major was the predominant diagnosis, accounting for 79 participants (68.7%), followed by HbS/β-thalassemia in 26 (22.6%) and sickle cell disease in 10 (8.7%). The median duration of transfusion therapy was 20.0 years (IQR, 12.0–30.0). Participants received a mean of 15.08 ± 2.06 transfusions annually, with a mean interval of 2.68 ± 0.67 weeks between transfusions (Table 1).

Table 1: Demographic and clinical characteristics of the study population (N=115)

Characteristic	n or n (%) or Mean ± SD or Median [IQR 25 - 75]
Total participants	115
Sex	
Male	59 (51.3%)
Female	56 (48.7%)
Age group	
<18 years	14 (12.2%)
18-30 years	57 (49.6%)
>30 years	44 (38.3%)
Diagnosis	
β-thalassemia major	79 (68.7%)
HbS/β-thalassemia	26 (22.6%)
Sickle cell disease	10 (8.7%)
Duration of transfusion therapy, years	20 [12.0-30.0]
Annual transfusion count	15.08 ± 2.06
Interval between transfusions, weeks	2.68 ± 0.67

3.2 Questionnaire responses and patient-reported outcomes

Fatigue and daily functioning

Fatigue represented a prominent component of the patient-reported burden. When asked to rate their current level of tiredness on a 5-point scale, the most frequently selected response was 3/5 (50; 43.5%), followed by 4/5 (21; 18.3%) and 2/5 (31; 27.0%). Eight patients (7.0%) reported the lowest level of fatigue (1/5), while 5 (4.3%) reported the highest level (5/5). The mean current fatigue score was 2.86 ± 0.99.

Importantly, 96 patients (83.5%) reported that fatigue affected their daily activities, whereas 19 (16.5%) did not report such an effect.

When asked to rate their usual daily fatigue, the most frequent response was again 3/5 (65; 56.5%), followed by 2/5 (23; 20.0%) and 4/5 (20; 17.4%). Four patients (3.5%) reported a score of 1/5 and three (2.6%) a score of 5/5. The mean daily fatigue score was 2.96 ± 0.89.

These findings indicate that fatigue was not merely a subjective symptom but was perceived by the majority of participants as interfering with everyday functioning.

Educational impact

A substantial proportion of participants perceived their illness as having affected their educational performance. One hundred and seven patients (93.0%) reported that their illness had affected or had previously affected their performance at school, while 8 (7.0%) did not report such an effect.

Despite this perceived impact, 102 patients (88.7%) reported that they had never failed a school subject because of their illness, whereas 13 (11.3%) reported having failed at least one subject.

Only 7 patients (6.1%) had repeated a school year, while 108 (93.9%) had not. Nevertheless, 21 patients (18.3%) reported having considered dropping out of school, suggesting that the educational burden may manifest not only through objective academic outcomes but also through thoughts about discontinuing education.

Self-rated academic performance showed a concentration around the intermediate categories. The most frequent rating was 2/5 (49; 42.6%), followed by 3/5 (42; 36.5%). Fourteen participants (12.2%) rated their academic performance as 4/5, six (5.2%) as 5/5, and four (3.5%) as 1/5. The mean self-rated academic performance score was 2.73 ± 0.96.

Social functioning and participation

Most participants reported maintaining close interpersonal relationships. 111 patients (96.5%) reported having a close friend, whereas 4 (3.5%) did not. On the other hand, 89 (77.4%) reported that they feel excluded or left out by their friends.

Participation in organized physical activity was very limited. Only 3 patients (2.6%) reported participating in sports, while 112 (97.4%) did not.

Night-time social activity was also limited. On a 5-point scale, 110 participants (95.7%) selected 1/5, indicating very low frequency of going out at night. Three (2.6%) selected 2/5 and two (1.7%) selected 3/5; no participant selected 4/5 or 5/5. The mean score was 1.06 ± 0.23.

Body image and self-perception

Satisfaction with physical appearance was generally concentrated in the lower-to-middle range. On the 5-point scale, 63 participants (54.8%) selected 2/5, while 34 (29.6%) selected 3/5. Seventeen participants (14.8%) selected 1/5, and only one participant (0.9%) selected 4/5. No participant selected 5/5.

The mean physical-appearance satisfaction score was therefore 2.17 ± 0.71, suggesting relatively limited satisfaction with physical appearance.

Furthermore, 113 patients (98.3%) reported that they compared themselves with others, while only 2 (1.7%) did not. Also, 101 (87.8%) reported that they thought other people judged them.

These findings indicate a pronounced concern with social comparison and perceived external judgment within the study population.

Emotional well-being

A substantial emotional burden was reported. 108 participants (93.9%) stated that they had experienced feelings of hopelessness, whereas 7 (6.1%) did not report such experiences.

This finding should be interpreted as a patient-reported emotional experience rather than evidence of clinically diagnosed depression or another psychiatric disorder, because the researcher-developed questionnaire was not a diagnostic instrument.

4. Future Perspectives

Despite the reported psychosocial burden, participants retained a considerable degree of enthusiasm regarding their future. On a 5-point scale assessing enthusiasm for future plans, 67 patients (58.3%) selected 2/5, 26 (22.6%) selected 3/5, 17 (14.8%) selected 1/5, and 5 (4.3%) selected 4/5. No participant selected 5/5. The mean score was 2.17 ± 0.73.

When asked whether they believed that the situation would be “fixed” within 20 years, only 15 participants (13.0%) answered yes, whereas 100 (87.0%) answered no.

At the same time, patients recognized the benefits of treatment. When asked to rate how much their life had improved since starting treatment, the most frequent responses were 2/5 and 3/5, each reported by 46 participants (40.0%). Fifteen patients (13.0%) selected 4/5, 5 (4.3%) selected 1/5, and 3 (2.6%) selected 5/5. The mean score was 2.70 ± 0.90.

Finally, all 115 participants (100%) reported that, if given the opportunity, they would wish not to have their illness.

Overall pattern of patient-reported burden

Taken together, the findings demonstrate a multidimensional burden extending beyond the hematological consequences of hemoglobinopathy. The most prominent reported concerns involved fatigue and interference with daily activities (83.5%), perceived effects on educational performance (93.0%), limited participation in sports (97.4%), very limited evening social activity, frequent social comparison (98.3%), perceived judgment by others (87.8%), and experiences of hopelessness (93.9%).

At the same time, the findings reveal an important contrast between recognition of treatment benefit and the persistent burden of living with the disease. Although all participants wished not to have the illness and most did not expect the situation to be resolved within 20 years, patients nevertheless reported some degree of perceived improvement following treatment.

Overall, the responses suggest that regular transfusion therapy may coexist with substantial psychosocial and functional challenges, emphasizing the importance of assessing patients' experiences beyond hematological parameters alone.

Table 2. Patient-reported burden and psychosocial impact across seven thematic domains (N = 115)

Domain	Questionnaire item	Response	n (%)
1. Fatigue and daily functioning	How tired do you feel today?	1 – Low	8 (7.0%)
		2	31 (27.0%)
		3	50 (43.5%)
		4	21 (18.3%)
		5 – High	5 (4.3%)
	Does fatigue affect your daily activities?	Yes	96 (83.5%)
		No	19 (16.5%)
	How would you rate your daily fatigue?	1 – Low	4 (3.5%)
		2	23 (20.0%)
		3	65 (56.5%)
		4	20 (17.4%)
		5 – High	3 (2.6%)
2. Educational impact	Does your illness affect/has it affected your performance in school?	Yes	107 (93.0%)
		No	8 (7.0%)
	Have you ever failed a subject because of your illness?	Yes	102 (88.7%)
		No	13 (11.3%)
	Have you ever repeated the same school year?	Yes	7 (6.1%)
		No	108 (93.9%)
	Have you ever thought about dropping out of school?	Yes	21 (18.3%)
		No	94 (81.7%)
	How would you rate your grades in school?	1 – Low	4 (3.5%)
		2	49 (42.6%)
		3	42 (36.5%)
		4	14 (12.2%)
		5 – High	6 (5.2%)
3. Social functioning and participation	Do you have any close friend?	Yes	111 (96.5%)
		No	4 (3.5%)
	Do you ever feel excluded or left out by your friends?	Yes	89 (77.4%)
		No	26 (22.6%)
	Do you participate in any sports?	Yes	3 (2.6%)
		No	112 (97.4%)
	How often do you go out at night?	1 – Low	110 (95.7%)
		2	3 (2.6%)
		3	2 (1.7%)
		4	0 (0%)
		5 – High	0 (0%)
4. Body image and self-perception	How satisfied are you with your physical appearance?	1 – Low	17 (14.8%)
		2	63 (54.8%)
		3	34 (29.6%)
		4	1 (0.9%)
		5 – High	0 (0%)
	Do you find yourself comparing yourself to others?	Yes	113 (98.3%)
		No	2 (1.7%)
	Do you think others judge you?	Yes	101 (87.8%)
		No	14 (12.2%)
5. Emotional well-being	Have you ever felt hopeless?	Yes	108 (93.9%)
		No	7 (6.1%)
6. Future perspectives	How enthusiastic are you about your future plans?	1 – Low	17 (14.8%)
		2	67 (58.3%)
		3	26 (22.6%)
		4	5 (4.3%)
		5 – High	0 (0%)
	Has your life changed for the better since you started treatment?	1 – Low	5 (4.3%)
		2	46 (40.0%)
		3	46 (40.0%)
		4	15 (13.0%)
		5 – High	3 (2.6%)
	Do you think that in 20 years, the situation will be fixed?	Yes	15 (13.0%)
		No	100 (87.0%)
7. Overall perceived illness acceptance	If you had the chance, would you wish you didn't have this illness?	Yes	115 (100%)
		No	0 (0%)

Correlates of patient-reported burden: Spearman rank correlation analysis

Spearman's rank correlation analysis (Table 3) demonstrated several significant associations between transfusion-related clinical parameters and quality-of-life domains among the 115 patients. After adjustment for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR), 23 of 35 associations remained statistically significant (FDR-adjusted $p < 0.05$).

Pretransfusion hemoglobin was inversely correlated with fatigue (r_s = -0.222, FDR-adjusted p = 0.033), daily activity limitations (r_s = −0.246, p = 0.019), and hopelessness (r_s = -0.201, p = 0.048), while it was positively correlated with appearance satisfaction (r_s = 0.326, p = 0.002). Its association with future enthusiasm did not remain significant after FDR correction (r_s = 0.189, p = 0.056).

Ferritin showed a positive correlation with fatigue (r_s = 0.347, FDR-adjusted p = 0.002) and daily activity limitations (r_s = 0.285, p = 0.007), as well as hopelessness (r_s = 0.208, p = 0.043). A negative association was observed with future enthusiasm (r_s = -0.224, p = 0.033).

Duration of transfusion was positively associated with fatigue (r_s = 0.303, FDR-adjusted p = 0.004), educational difficulties (r_s = 0.250, p = 0.018), social restriction (r_s = 0.204, p = 0.046), and hopelessness (r_s = 0.344, p = 0.002), while it was inversely associated with future enthusiasm (r_s = -0.309, p = 0.003).

Annual transfusion frequency demonstrated positive correlations with fatigue (r_s = 0.336, FDR-adjusted p = 0.002), daily activity limitations (r_s = 0.213, p = 0.041), educational difficulties (r_s = 0.274, p = 0.010), social restriction (r_s = 0.255, p = 0.016), and appearance satisfaction (r_s = -0.209, p = 0.043 as well as future enthusiasm (r_s = -0.234, p = 0.026).

Finally, longer transfusion intervals were significantly associated with fewer daily activity limitations (r_s = -0.357, FDR-adjusted p = 0.002), fewer educational difficulties (r_s = -0.328, p = 0.002), less social restriction (r_s = -0.266, p = 0.012), and less hopelessness (r_s = -0.321, p = 0.002). The correlations with fatigue (r_s = -0.194, p = 0.053), appearance

satisfaction (r_s = 0.150, p = 0.120), and future enthusiasm (r_s = 0.158, p = 0.106) were not significant after FDR correction.

Table 3: Spearman correlations between transfusion-related parameters and quality-of-life domains

Clinical Parameter	Fatigue	Daily activity limitations	Educational difficulties	Social restriction	Appearance satisfaction	Hopelessness	Future enthusiasm
Pretransfusion Hb	−0.222 / 0.033	−0.246 / 0.019	0.118 / 0.215	0.159 / 0.106	0.326 / 0.002	−0.201 / 0.048	0.189 / 0.056
Ferritin	0.347 / 0.002	0.285 / 0.007	0.136 / 0.156	0.093 / 0.323	−0.157 / 0.106	0.208 / 0.043	−0.224 / 0.033
Duration of transfusion	0.303 / 0.004	0.196 / 0.052	0.250 / 0.018	0.204 / 0.046	−0.173 / 0.081	0.344 / 0.002	−0.309 / 0.003
Annual transfusion	0.336 / 0.002	0.213 / 0.041	0.274 / 0.010	0.255 / 0.016	−0.209 / 0.043	0.191 / 0.055	−0.234 / 0.026
Transfusion interval	−0.194 / 0.053	−0.357 / 0.002	−0.328 / 0.002	−0.266 / 0.012	0.150 / 0.120	−0.321 / 0.002	0.158 / 0.106

Note: Values are presented as Spearman's rank correlation coefficient (r_s) / Benjamini–Hochberg FDR-adjusted two-sided p-value; N = 115. Bold values indicate FDR-adjusted p<0.05.

Factors associated with high patient-reported burden: Multivariable logistic regression analysis

For logistic regression analyses, the patient-reported outcomes were dichotomized according to the original questionnaire response categories. For daily activity impairment, responses to "Does fatigue affect your daily activities?" were coded as 1 for "Yes" and 0 for "No." For educational impairment, responses to "Does your illness affect/has it affected your performance in school?" were coded as 1 for "Yes" and 0 for "No." For patient-reported hopelessness, responses to "Have you ever felt hopeless?" were coded as 1 for "Yes" and 0 for "No." The distribution of outcome events and non-events used in each logistic regression model is presented in Supplementary Table S1. Given the high prevalence of these outcomes, particularly educational impairment and hopelessness, the relatively small number of non-events should be considered when interpreting the precision and stability of the corresponding regression estimates.

Supplementary Table S1. Coding and distribution of binary outcomes used in logistic regression analyses

Regression outcome	Original questionnaire item	Response coded as 1 (event)	Response coded as 0 (non-event)	Events, n (%)	Non-events, n (%)
Daily activity impairment	Does fatigue affect your daily activities?	Yes	No	96 (83.5%)	19 (16.5%)
Educational impairment	Does your illness affect/has it affected your performance in school?	Yes	No	107 (93.0%)	8 (7.0%)
Patient-reported hopelessness	Have you ever felt hopeless?	Yes	No	108 (93.9%)	7 (6.1%)

Note: For all models, 1 indicated presence of the outcome and 0 indicated absence of the outcome. Events represent participants coded as 1 and non-events represent participants coded as 0. Percentages are based on the total study population (N=115).

Daily activity impairment

In univariable logistic regression, age, diagnosis, ferritin >2500 ng/mL, transfusion interval, and pretransfusion Hb were significantly associated with daily activity impairment (Table 4). In the multivariable model, all five variables remained independently associated with the outcome. Each 10-year increase in age was associated with higher odds of daily activity impairment (adjusted OR 2.94, 95% CI 1.34–6.44; p=0.007). TM was associated with higher odds compared with SCD (adjusted OR 2.44, 95% CI 1.11–5.35; p=0.026), while ferritin >2500 ng/mL was independently associated with increased odds (adjusted OR 2.77, 95% CI 1.26–6.07; p=0.011). Longer transfusion intervals and higher pretransfusion Hb were associated with lower odds of impairment (adjusted OR 0.27 and 0.43, respectively).

Table 4: Univariable and multivariable logistic regression analysis of factors associated with daily activity impairment

Clinical Parameter	Univariable OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age, per 10-year increase	2.25 [1.03 - 4.92]	0.043	2.94 [1.34 - 6.44]	0.007
Diagnosis: TM vs SCD	3.73 [1.70 - 8.17]	<0.001	2.44 [1.11 - 5.35]	0.026
Ferritin >2500 vs ≤2500 ng/mL	2.34 [1.07 - 5.12]	0.034	2.77 [1.26 - 6.07]	0.011
Transfusion interval, per 2-week increase	0.33 [0.15 - 0.71]	0.005	0.27 [0.12 - 0.57]	0.001
Pretransfusion Hb, per 1 g/dL increase	0.39 [0.18 - 0.86]	0.019	0.43 [0.19 - 0.94]	0.033

Abbreviations: OR, odds ratio; CI, confidence interval; Hb, hemoglobin; TM, transfusion-dependent β-thalassemia; SCD, sickle cell disease.

5. Educational impairment

In multivariable logistic regression, older age was independently associated with increased odds of educational impairment, whereas longer transfusion intervals and higher pretransfusion hemoglobin were associated with lower odds (Table 5). Each 10-year increase in age increased the odds of educational impairment by approximately 2.4-fold (adjusted OR 2.36, 95% CI 1.08–5.17; p=0.032). Conversely, each 2-week increase in transfusion interval was associated with 65% lower odds (adjusted OR 0.35, 95% CI 0.16–0.77; p=0.008), while each 1 g/dL increase in pretransfusion hemoglobin was associated with 56% lower odds (adjusted OR 0.44, 95% CI 0.20–0.96; p=0.040). Neither diagnosis nor ferritin >2500 ng/mL remained statistically significant after adjustment.

Table 5: Univariable and multivariable logistic regression analysis of factors associated with educational impairment

Clinical Parameter	Univariable OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age, per 10-year increase	2.03 [0.93 - 4.44]	0.077	2.36 [1.08 - 5.17]	0.032
Diagnosis: TM vs SCD	1.59 [0.73 - 3.49]	0.245	1.97 [0.90 - 4.31]	0.194
Ferritin >2500 vs ≤2500 ng/mL	1.92 [0.87 - 4.20]	0.104	1.68 [0.77 - 3.68]	0.091
Transfusion interval, per 2-week increase	0.42 [0.19 - 0.91]	0.028	0.35 [0.16 - 0.77]	0.008
Pretransfusion Hb, per 1 g/dL increase	0.48 [0.22 - 1.05]	0.069	0.44 [0.20 - 0.96]	0.040

Emotional burden

In multivariable logistic regression analysis, older age and severe iron overload were independently associated with increased odds of patient-reported hopelessness, whereas longer transfusion intervals and higher pretransfusion hemoglobin were associated with lower odds (Table 6). Each 10-year increase in age was associated with a 2.73-fold increase in the odds of patient-reported hopelessness (adjusted OR 2.73, 95% CI 1.25–5.99; p=0.012). Ferritin >2500 ng/mL was also independently associated with increased odds of patient-reported hopelessness (adjusted OR 2.28, 95% CI 1.04–5.00; p=0.039). Conversely, each 2-week increase in transfusion interval was associated with a 67% reduction in the odds of patient-reported hopelessness (adjusted OR 0.33, 95% CI 0.15–0.73; p=0.006), while each 1 g/dL increase in pretransfusion hemoglobin was associated with a 56% reduction in odds (adjusted OR 0.44, 95% CI 0.20–0.96; p=0.039). Diagnosis was not independently associated with patient-reported hopelessness (p=0.180).

Table 6: Univariable and multivariable logistic regression analysis of factors associated with patient-reported hopelessness

Clinical Parameter	Univariable OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age, per 10-year increase	2.42 [1.11 - 5.31]	0.027	2.73 [1.25 - 5.99]	0.012
Diagnosis: TM vs SCD	1.93 [0.91 - 4.35]	0.099	1.71 [0.78 - 3.75]	0.180
Ferritin >2500 vs ≤2500 ng/mL	1.99 [0.91 - 4.35]	0.086	2.28 [1.04 - 5.00]	0.039
Transfusion interval, per 2-week increase	0.39 [0.18 - 0.85]	0.018	0.33 [0.15 - 0.73]	0.006
Pretransfusion Hb, per 1 g/dL increase	0.39 [0.18 - 0.86]	0.020	0.44 [0.20 - 0.96]	0.039

6. Discussion

The present study aimed to describe the experience of burden among 115 Albanian patients with transfusion-dependent hemoglobinopathies. All of them had received regular blood transfusions for a considerable period of time with a median duration of treatment being 20 years. Patients received 15 transfusions per year on average or about every 2.68 weeks. The reported burden extended across multiple domains, including fatigue, daily functioning, education, social participation, body image, emotional well-being, and future perspectives. Similar multidimensional effects have been reported among transfusion-dependent patients in Greece, Italy, Turkey, Iran, Egypt, Qatar, Lebanon, and multinational studies.

6.1 Principal findings and the relevance of long-term treatment exposure

Almost 88% of participants were adults, reflecting substantial disease and treatment exposure. This may partly explain the burden observed compared with predominantly pediatric cohorts. In a large Greek multinational cross-sectional study (Klonizakis P, et al.) of 283 adult patients with transfusion dependent thalassemia, age was found to be the single most important determinant of poorer health-related quality of life (HRQOL) and employment was independently associated with better HRQOL [7]. An Italian survey of TD patients aged ≥14 years also found that compared to the general population, TD patients reported a worse status in physical functioning, energy/vitality, social functioning, bodily pain, and general health domains (Tedone F, et al.) [8]. In the present study, longer transfusion duration was associated with greater fatigue, educational and social limitations, hopelessness, and reduced optimism. However, these associations should not be interpreted as a direct effect of transfusions. Treatment duration likely represents cumulative disease exposure, aging, complications, prolonged treatment requirements, and the psychological burden of living with a chronic condition. This interpretation is consistent with studies identifying complications, comorbidities, and long-standing disease as important determinants of HRQOL.

6.2 Fatigue, hemoglobin control, and daily functioning

Fatigue was one of the most clinically relevant findings, with 83.5% of participants reporting interference with daily activities. Italian β-thalassemia patients who required regular blood transfusions had a considerably lower vitality/energy score than the general population, and comparable results were found in Greece, Turkey, Iran. All of these populations had a substantial decrease in physical functioning and activity levels compared to healthy controls [7, 8, 9, 10]. Thus, the study's primary conclusion aligns with existing literature regarding the impacts of thalassemia major on patients' physical functionality and activity levels. It must be added that fatigue often occurs alongside tiredness, weakness, and other symptoms of anemia.

The association between pretransfusion hemoglobin and fatigue or activity limitation is biologically plausible because hemoglobin availability influences tissue oxygenation and physical performance. The study's results correspond with a substantial body of evidence linking anemia to patient-reported limitations in physical activity, with tiredness, fatigue, and feeling weak being the most common symptoms of low hemoglobin [11]. Specifically, the Iranian study (Etemad K, et al.) of 1,240 patients found that hemoglobin was one of the variables associated with patients' quality of life [12].

In our multivariable analysis, higher pretransfusion hemoglobin was associated with lower odds of impairment in daily activity, education, and hopelessness. Nevertheless, causality cannot be established because hemoglobin levels

may also reflect adherence, healthcare access, socioeconomic factors, disease severity, and complications. Therefore, hemoglobin should be considered as part of a broader clinical assessment rather than as an isolated modifiable determinant.

6.3 Iron overload as a potential contributor to multidimensional burden

Higher ferritin was associated with greater fatigue, activity limitation, and hopelessness and with lower future optimism. Ferritin >2500 ng/mL was independently associated with activity impairment and hopelessness. The relationships between iron burden and patient-reported outcomes could be explained by the direct impact of iron overload on organ dysfunction and physical disability as well as indirect effects on treatment intensity, perception of risk, and other factors that influence patients' quality of life. These findings are consistent with previous studies. The study conducted in Turkey (Tuysuz G, et al.) revealed that high ferritin was the sole indicator of impaired overall health-related quality of life in a multivariate model, whereas the Iranian study (Khodashenas M, et al.) found that lower ferritin levels were independently associated with higher quality of life scores [10, 13]. Similar results were also reported in an Egyptian pediatric study, which identified high ferritin as a predictor of poor social quality of life [14]. A systematic review (Lee WJ, et al.), also reported a generally consistent, although still limited, association between increased ferritin and poorer clinical or patient-reported outcomes [15].

However, ferritin should not be interpreted as a direct causal determinant of emotional well-being. It reflects cumulative transfusion exposure, iron-related morbidity, chelation intensity, inflammation, and other clinical factors. Thus, the findings support optimal iron-overload management as one component of a comprehensive strategy to reduce disease burden. This is also consistent with evidence linking better chelation adherence with lower ferritin and improved HRQOL [15].

6.4 Educational impact: perceived impairment exceeds objective academic disruption

A notable finding was the discrepancy between perceived and objective educational impact. Although 93.0% of participants believed that their illness affected school performance, relatively few had failed a subject or repeated a grade. Chronic transfusion requirements, fatigue, reduced concentration, absenteeism, hospitalization, anxiety, and social isolation may affect educational experience even when formal academic progression is maintained.

The study supports the results of pediatric studies conducted in Egypt (Hakeem GLA, et al.), Turkey (Tuysuz G, et al.), Qatar (Nashwan AJ, et al.), and Iran (Bazi A, et al.), showing that children with transfusion-dependent thalassemia had lower school performance compared to healthy peers [10, 14, 16, 17]. In the international SWAY survey, children and adults with sickle cell disease reported that school functioning was highly impacted (51% had a negative effect on school performance) [18].

In the current study, higher pretransfusion hemoglobin and longer transfusion intervals were associated with lower educational impairment. Although the relationship with hemoglobin is plausible, a longer interval may simply reflect lower treatment burden, less severe disease, or different transfusion targets. Therefore, these findings should not be interpreted as evidence that transfusions should be administered less frequently. Individualized management should balance hematological targets with treatment burden.

6.5 Social participation, isolation, and body image

The social findings suggest selective rather than complete social isolation. Most participants reported having a close friend, but participation in sports and nighttime social activities was very limited.

The pattern is similar to the findings in Italy (Tedone F, et al.), Greece, Turkey, Iran (Bazi A, et al.), Egypt, and Qatar. The social function score was lower for Italian patients compared to the general population and was among the lowest for Iranians for pediatric patients [8, 17]. Lack of sports participation for the Turkish patients (Töret E, et al.) can be explained by various factors: anemia-associated symptoms, avoidance of exacerbating activities, other treatment limitations, time constraints due to treatment, parental restrictions, and/or lack of motivation [9]. The study noted no significant differences between groups regarding sports participation; thus, it is impossible to say with a high degree of confidence whether any particular category of patients was significantly more socially limited due to a particular cause.

Participants also reported low-to-moderate satisfaction with physical appearance and frequent comparison with others or feelings of being judged. Chronic hemoglobinopathies may affect body image through short stature, skeletal changes, delayed puberty, treatment effects, and disease complications. However, our study did not assess which specific physical or social factors contributed to body-image dissatisfaction, so these explanations remain hypothetical. The same can be said about other potential interactions that could affect body image, such as the restrictions affecting employment, education, or socialization, which were previously reported in the literature for people with thalassemia [9, 19, 20].

The observed associations between pretransfusion hemoglobin, transfusion frequency, and appearance satisfaction should likewise be interpreted cautiously because reverse causation and unmeasured confounding are possible.

6.6 Emotional burden and future perspectives

Reported hopelessness and negative perceptions of the future were among the most striking findings. These results should not be equated with depression or another psychiatric disorder because the researcher-developed questionnaire was not a validated mental-health screening instrument. Nevertheless, they indicate an important emotional burden that warrants further clinical evaluation.

Studies conducted in Turkey (Töret E, et al.) and Iran (Haghpanah S, et al.), (Adib-Hajbaghery M, et al.) confirm the poorer psychological wellbeing and higher rates of

depression symptoms among β-thalassemia patients compared to the general population [9, 19, 21]. The Italian study similarly reported worse levels of overall psychological wellbeing, while Greek and Egyptian research highlights the role of age, complications, and burden on health-related quality of life [7, 8, 14].

In our multivariable analysis, older age and severe iron overload were independently associated with greater odds of patient-reported hopelessness, whereas higher pretransfusion hemoglobin and longer transfusion intervals were associated with lower odds. The association with age is consistent with Greek evidence (Klonizakis P, et al.) showing an adverse effect of increasing age on quality of life [7]. A plausible explanation is cumulative disease exposure and the progressive recognition of long-term health, occupational, reproductive, and social challenges. Nevertheless, the very high prevalence of reported hopelessness may also reflect the wording and response structure of the questionnaire; therefore, this result should be interpreted as a measure of patient-reported emotional experience rather than as a population estimate of psychiatric morbidity.

The apparent paradox that many patients felt treatment had improved their condition while remaining pessimistic about the future may reflect a distinction between benefiting from treatment and perceiving the underlying disease as a lifelong limitation. Similar data were reported in the Italian, Greek, and multinational studies evaluating the health-related quality of life of β-thalassemia patients [7, 8, 22].

6.7 Clinical implications

Overall, the study results help conceptualize the patient burden as being determined by a combination of biological and treatment-related mechanisms. Indeed, the analysis revealed that higher pre-transfusion hemoglobin levels were associated with better outcomes, whereas increased ferritin levels and longer treatment duration were independently linked to various negative outcomes. These findings challenge the traditional perspective on long-term transfusion therapy outcomes, highlighting the need to evaluate transfusion-dependent thalassemia patients beyond mere survival, hemoglobin levels, and standard biochemical markers.

The study results can guide the development of appropriate interventions in the context of Albania. First of all, a routine, short screening test should be designed and implemented to assess patients' fatigue, functionality, school or work performance, social behavior, body image, and mental health. At the same time, international studies highlight the need for a more comprehensive evaluation of transfusion-dependent patients who survive for decades after the disease onset [15, 23]. In particular, an interdisciplinary approach to follow-up care may be beneficial in the identified context, combining health care, psychological, educational, and social interventions and focusing on the enhancement of patients' physical activity and social engagement.

7. Strengths and Limitations

A major strength of this study is the integration of descriptive patient-reported outcomes with correlation and multivariable analyses in a cohort with substantial long-term transfusion exposure. The application of Benjamini–Hochberg correction also reduced the likelihood that the reported correlation findings were attributable to multiple testing alone. The study further provides data from Albania, a setting underrepresented in the international literature on patient-reported burden in transfusion-dependent hemoglobinopathies.

There are a few limitations that deserve mention. First, due to the cross-sectional design, no causal relationships could be established. In addition, the questionnaire was developed by the researchers specifically for this study and was not validated against established instruments such as TranQol, SF-36, WHOQOL-BREF, or PedsQL, limiting direct comparison with previous studies. Several questionnaire items also produced highly prevalent affirmative responses, which may partly reflect item wording or response structure rather than the full spectrum of participant experiences. This high prevalence resulted in relatively few non-events for some logistic regression outcomes, particularly educational impairment and hopelessness, which may have reduced the stability and precision of the corresponding multivariable estimates; therefore, these findings should be interpreted cautiously and confirmed in larger cohorts using validated patient-reported outcome measures. Furthermore, the sample included several disease subtypes, while the number of patients with sickle cell disease was relatively small, precluding reliable disease-specific analyses. Finally, residual confounding from clinical complications, socioeconomic status, educational attainment, treatment adherence, pain, and psychiatric comorbidities cannot be excluded.

8. Conclusions

Transfusion-dependent hemoglobinopathies were associated with substantial patient-reported burden across fatigue, daily functioning, education, social participation, self-perception, emotional well-being, and future perspectives. Several clinical and transfusion-related characteristics, including pretransfusion hemoglobin, iron burden, treatment exposure, and transfusion interval, were associated with selected outcomes, although causal relationships cannot be inferred. These findings support incorporating patient-reported assessment and multidisciplinary psychosocial support into long-term care. Longitudinal studies using validated disease-specific instruments are needed to determine whether optimized clinical and organizational care improves psychosocial and functional outcomes.

Conflict of interest

The authors declare that they have no conflicts of interest related to this study.

Author Contributions

THD conceived and designed the study, collected and analyzed the data, interpreted the findings, and drafted the manuscript. MK contributed to study design, data interpretation, and critical revision of the manuscript. Both

authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Ethical approval
Ethical approval was obtained from the National Agency for Scientific Research and Innovation and the Ethics Council of the University of Medicine, Tirana, Albania. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed consent
Written informed consent was not required. Participants were informed about the study and provided verbal consent to participate and complete the questionnaire, in accordance with the protocol approved by the relevant ethics committees.

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Language Assistance
Google Translate was used to facilitate the translation of the questionnaires from Albanian into English. The translations were subsequently reviewed and refined by the authors to ensure linguistic accuracy, clarity, and consistency with the original Albanian version. The authors take full responsibility for the scientific content, interpretation of the data, and final manuscript.

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