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Blood transfusion therapy for β-thalassemia major and hemoglobin E β-thalassemia: Adequacy, trends, and determinants in Sri Lanka

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Abstract

Background: Regular blood transfusion therapy still remains the cornerstone in the management of β-thalassemia. Although recommendations are clear for patients with β-thalassemia major, uniform transfusion guidelines are lacking for patients with hemoglobin E β-thalassemia. In this study, we aim to describe the adequacy, trends, and determinants of blood transfusion therapy in a large cohort of pediatric patients with β-thalassemia major and hemoglobin E β-thalassemia.

Methods/procedure: This cross-sectional study was performed among all regularly transfused patents with β-thalassemia aged 2 to 18 years attending three large thalassemia centers in Sri Lanka. Data were collected using an interviewer-administered questionnaire, perusal of clinical records, and physical examination of patients by trained doctors.

Results: A total of 328 patients (male 47%) were recruited; 83% had β-thalassemia major, whereas 16% had hemoglobin E β-thalassemia. Sixty-one percent of patients had low pretransfusion hemoglobin levels (< 9.0 g/dL) despite receiving high transfusion volumes (> 200 mL/kg/year) by a majority (56%). Median pretransfusion hemoglobin was significantly lower in patients with hemoglobin E β-thalassemia compared with β-thalassemia major ($P < 0.001$); however, there was no difference in requirement for high transfusion volumes over 200 mL/kg/year in both groups ($P = 0.14$). Hepatomegaly and splenomegaly were more common in hemoglobin E β-thalassemia and were associated with lower pretransfusion hemoglobin. Transfusion requirements were higher among patients with hepatitis C and in those who are underweight.

Conclusions: Over 60% of regularly transfused patients with β-thalassemia have low pretransfusion hemoglobin levels despite receiving large transfusion volumes. Patients with hemoglobin E β-thalassemia are undertransfused and specific recommendations should be developed to guide transfusions in these patients.

KEYWORDS

Beta-thalassemia major, hemoglobinopathies, thalassemia, transfusion

1 | INTRODUCTION

β-Thalassemia is a disorder of hemoglobin synthesis, which is characterized by chronic anemia in affected individuals.[1] The genetic defects are point mutations located in and around the β-globin gene that demonstrate autosomal recessive inheritance.[2] Most patients are transfusion dependent and require regular blood transfusions to counteract anemia.[3] The only available cure for thalassemia is stem cell transplantation; however, it is not available to a majority of patients due to limitations in suitable donors and cost.[4] Therefore, a vast majority of patients with β-thalassemia, those who live in developing countries in particular, are managed medically with regular blood transfusions and iron chelation for life.[5]

Abbreviation: HbE, hemoglobin E

Medical management of β-thalassemia has improved considerably during the past few years owing to the availability of safe blood products and effective oral iron chelators.[6–8] Many patients with β-thalassemia major thus survive beyond the fourth decade and have fewer rates of complications due to anemia or iron overload.[5] Indications to commence and recommendations to guide regular transfusions are unambiguous for patients with β-thalassemia major and are clearly laid down in the management guidelines of the Thalassemia International Federation.[9] These guidelines recommend regular transfusions every 2 to 5 weekly to maintain pretransfusion hemoglobin levels between 9.0 and 10.5 g/dL in patients with transfusion-dependent β-thalassemia.

In contrast, clear guidelines are lacking to guide transfusions in patients with hemoglobin E (HbE) β-thalassemia, which is a heterogeneous disease with a variable degree of clinical severity.[10] Although some guidelines recommend categorizations of patients with HbE β-thalassemia into mild, moderate, and severe, these categorizations are arbitrary and inconclusive with significant overlap and shifting of patients between categories. Due to these reasons, it has been extremely difficult to develop uniform guidelines on transfusion therapy for patients with HbE β-thalassemia. Therefore, it is timely to evaluate the adequacy and patterns of transfusion therapy in patients with β-thalassemia major and HbE β-thalassemia.

A majority of studies that evaluate the clinical course, management, and complications of β-thalassemia were published several years back, specially in an era where patients were not surviving beyond their 20s.[11–13] Most interest during recent years has been on the development of novel therapies for β-thalassemia[14–18] and to study changing patterns of complications of nontransfusion-dependent thalassemia.[19] Due to these reasons, large-scale studies that evaluate the effects, kinetics, and outcomes of blood transfusion therapy in regularly transfused patients with severe thalassemia during recent years are sparse.

Sri Lanka is a low-middle-income country located in South Asia within the tropical belt where β-thalassemia is highly prevalent.[20] The gene frequency of β-thalassemia in Sri Lanka is reported as 2.8%, and approximately 2000 patients with severe β-thalassemia are managed in several thalassemia centers across the country.[21] However, a vast majority of patients (over two thirds) are managed in three large tertiary referral centers, namely, Kurunegala, Anuradhapura, and Ragama thalassemia centers, which are located in three different provinces to serve the entire country. In this study, we aim to describe the adequacy, trends, and determinants of blood transfusion therapy in a large cohort of pediatric patients with β-thalassemia major and HbE β-thalassemia in Sri Lanka.

2 | METHODS

This cross-sectional study was performed in three large thalassemia centers of Sri Lanka from September to December 2017. All patients with β-thalassemia who were transfused regularly and aged between 2 and 18 years attending Kurunegala, Anuradhapura, and Ragama thalassemia centers during the study period were recruited into the study. The diagnosis of thalassemia was based on hemoglobin subtype quantification using high-performance liquid chromatography prior to commencement of transfusions and "regular transfusions" was defined as receiving transfusions more frequently than 6 weekly. Parents of the participants were briefed about the study, and informed written consent from guardians and assent from children over 12 years were obtained before recruiting into the study.

Data were collected using an interviewer-administered questionnaire, perusal of clinical records, and physical examination of patients. After recruitment, a trained data collector interviewed patients and their parents to gather data on basic demographics, parental education level and occupations, monthly family income, previous hospital stays, transfusion history, and transfusion reactions. Then, clinical records of participants were perused to gather information on pretransfusion hemoglobin levels during previous 6 months and the volume of blood transfused during the preceding 12 months. Next, physical examinations were performed by trained doctors to measure anthropometric parameters and liver and spleen sizes. Weights were measured using a calibrated beam balance while height measurements were done using a stadiometer. Underweight and short stature were defined as having weight or height less than −2 standard deviation for age and sex in World Health Organisation growth standards.

Annual transfusion requirement (mL/kg/year) was calculated as total volume of blood (mL) transfused during the past one year divided by body weight (kg). The standard hematocrit of leucocyte-depleted packed red blood cells used for transfusions of these patients was 75%. Data were analyzed using IBM SPSS statistics 25.0 for windows. Mann–Whitney *U* test, χ^2 test, and multiple logistic regression were used in the analysis. Ethical approval was obtained from the Ethics Review Committee of University of Kelaniya, Sri Lanka.

3 | RESULTS

A total of 328 patients were recruited into the study, of which 153 (46.6%) were males and 175 (53.4%) were females. Numbers of patients who belonged to different age categories were 2 to 4 years, 45 (13.7%); 5 to 7 years, 73 (22.3%); 8 to 12 years, 118 (36.0%); and 13 to 18 years, 92 (28.0%). Proportions of patients from each thalassemia center were Kurunegala, 192 (58.5%); Anuradhapura, 94 (28.7%); and Ragama, 42 (12.8%). The clinical diagnosis of a majority (272; 82.9%) of patients was β-thalassemia major (homozygous β-thalassemia), whereas 53 (16.2%) had HbE β-thalassemia. Three (0.9%) patients had other forms of thalassemia, of which two had heterozygotes β-thalassemia mutation with triplicated α-globin genes and the other had sickle β-thalassemia.

3.1 | Adequacy of blood transfusions

All patients received regular blood transfusions at 2 to 5 weekly intervals (Table 1). Pretransfusion hemoglobin levels of the study population ranged between 4.6 and 11.7 g/dL, with a mean of 8.3 (± 1.2) g/dL. Only 119 (39%) patients had average pretransfusion hemoglobin levels above 9.0 g/dL over the preceding six months. The median pretransfusion hemoglobin level of patients with HbE β-thalassemia was significantly lower than that of β-thalassemia major

TABLE 1 Clinical characteristics related to transfusion therapy

Characteristic	Number ($n = 328$)	Percentage
Frequency of blood transfusion		
2 weekly	1	0.3
3 weekly	39	11.9
4 weekly	251	76.5
5 weekly	37	11.3
Average pretransfusion hemoglobin		
<7.0 g/dL	48	14.6
7.0–8.9 g/dL	151	46.0
9.0–10.5 g/dL	117	35.7
>10.5 g/dL	12	3.7
Annual transfusion requirement[a]		
<200 mL/kg/year	135	43.7
201–250 mL/kg/year	49	15.9
251–300 mL/kg/year	65	21.0
>300 mL/kg/year	60	19.4
Spleen status		
No splenomegaly	211	64.4
Splenomegaly of 1–3 cm	97	29.6
Splenomegaly of ≥ 4 cm	13	4.0
Splenectomized	7	2.1
Liver status		
No hepatomegaly	223	68.0
Hepatomegaly of 1–2 cm	86	26.2
Hepatomegaly ≥3 cm	19	5.8
Transfusion reactions		
Yes	260	79.2
No	68	20.8
Transfusion-transmitted infections		
No transfusion-transmitted infections	259	79.0
Hepatitis C infection	69	21.0
Weight[b]		
Normal weight	197	67.0
Underweight	97	33.0
Height[c]		
Normal height	168	56.8
Short stature	128	43.2

Missing data: [a]19 subjects; [b]34 subjects; and [c]32 subjects.

(7.0 vs 8.7 mg/dL, $P < 0.001$) (Figure 1). Almost all patients (51, 96.2%) with HbE β-thalassemia had median pretransfusion hemoglobin less than 9 g/dL, whereas 145 (53.3%) patients with β-thalassemia major had pretransfusion hemoglobin below 9 g/dL (Table 2).

Evaluation of annual transfusion requirements of patients revealed a wide range from 68 to 744 mL/kg/year, with a mean of 235(± 80) mL/kg/year. A large proportion of patients (56%) had high transfusion requirements, which was defined as greater than 200 mL/kg/year. The median annual transfusion requirement of patients with HbE β-thalassemia was lower than that of patients with β-thalassemia major (188 vs 223 mL/kg/year) (Figure 1). However, there was no significant difference in the requirement for high transfusion volumes (>200 mL/kg/year or > 300 mL/kg/year) between β-thalassemia major and HbE β-thalassemia patient groups (Table 2).

3.2 | Clinical parameters that affect blood transfusions

A majority of patients in our study population (196; 59.7%) did not have hepatosplenomegaly (Table 1). Splenomegaly was detected in 110 (33.6%) patients, of which 13 (4.0%) had spleens which were larger than 3 cm. The total number of patients with hepatomegaly was 105 (32.0%) and 19 (5.8%) patients had livers that were larger than 3 cm. Significantly higher proportion patients with HbE β-thalassemia had splenomegaly (67.9% vs 26.8%, $P < 0.001$) and hepatomegaly (58.5% vs 26.8%, $P < 0.001$) when compared with patients with β-thalassemia major (Table 2).

Next, we evaluated pretransfusion hemoglobin levels and annual transfusion requirements of patients with and without hepatomegaly or splenomegaly (Figure 1). This revealed that pretransfusion hemoglobin levels of patients with splenomegaly and hepatomegaly were significantly lower compared with patients without organomegaly. Additionally, median annual transfusion requirements were significantly higher among patients with hepatitis C infection and in those who are underweight. History of transfusion reactions and short stature did not have significant associations with pretransfusion hemoglobin levels or annual transfusion requirements.

3.3 | Transfusion requirement with age

In this study population, we did not observe significant changes in pretransfusion hemoglobin levels with age ($R = 0.07$, $P = 0.21$) (Figure 2). Similarly, annual transfusion requirements remained steady throughout aging ($R = 0.003$, $P = 0.47$). Correlation between pretransfusion hemoglobin levels and annual transfusion requirements showed significant albeit trivial negative correlation ($R = -0.1$, $P < 0.05$).

3.4 | Sociodemographic factors affecting optimal blood transfusions status

Finally, we performed multiple logistic regression to identify independent predictors of optimal blood transfusion status, which was defined as having an average pretransfusion hemoglobin above 9.0 g/dL over the past six months. This revealed that higher social class based on paternal occupation is associated with higher pretransfusion hemoglobin levels and optimal blood transfusion status (Table 3). Sex, maternal education level, family income, or duration of hospital stay were not significantly associated with optimal blood transfusion status.

4 | DISCUSSION

This study is one of the largest recent studies on the adequacy of blood transfusion among patients with β-thalassemia. We studied 328

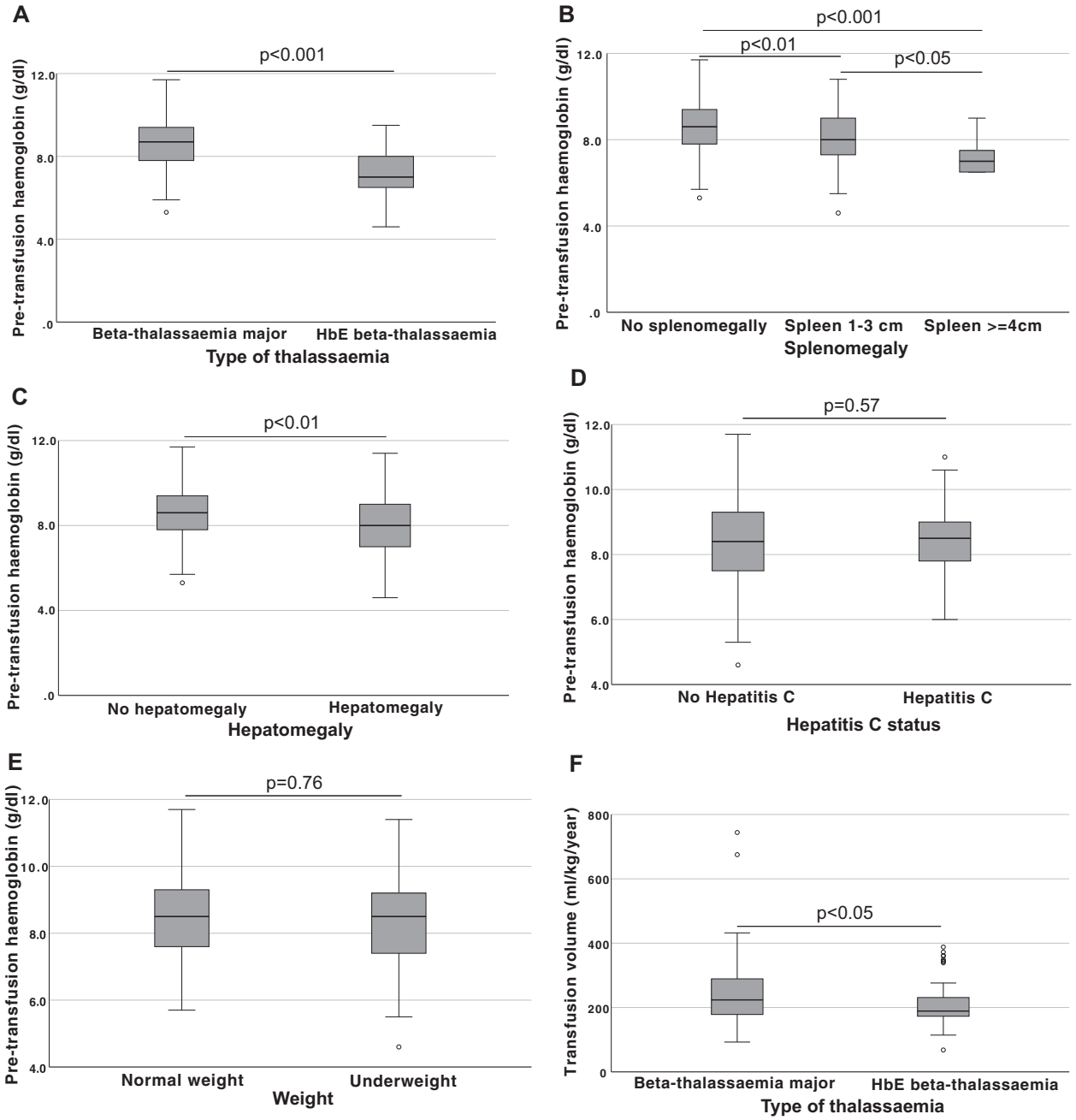

FIGURE 1 Pretransfusion hemoglobin levels (A–E) and annual transfusion requirements (F–J) of patients with different clinical situations. Each box plot shows interquartile range; middle horizontal bars demonstrate respective median and error bars show range; outliers are marked in circles. *P* values are calculated using the Mann–Whitney *U* test

regularly transfused patients aged between 2 and 18 years in three large thalassemia centers in Sri Lanka, which represent more than two thirds of the patient population in the country.[22] All three centers have free and unlimited access to blood products through a state-run National Blood Transfusion Service[9]; therefore, data presented here uniquely represent best possible management in a nonresource limited setting in terms of blood transfusions where access to healthcare is free and equal.

One striking observation of our study is that despite free access to blood products, over 60% of patients did not maintain pretransfusion hemoglobin levels above 9.0 g/dL. This is more pronounced among patients with HbE β-thalassemia who had significantly lower pretransfusion hemoglobin levels compared with patients with β-thalassemia major. This was despite receiving over 200 mL/kg/year blood volumes by a majority of patients. Annual transfusion requirements of patients in our cohort were greater than the values reported by other centers; recently, Casale et al reported that the average blood consumption by regularly transfused patients with β-thalassemia as 188 mL/kg/year.[23] This paradox of suboptimal pretransfusion hemoglobin levels and high transfusion requirement cannot be explained by splenomegaly as only a minority (4%) of patients were having splenomegaly of 4 cm or more. Therefore, several other non-patient-related factors that include time

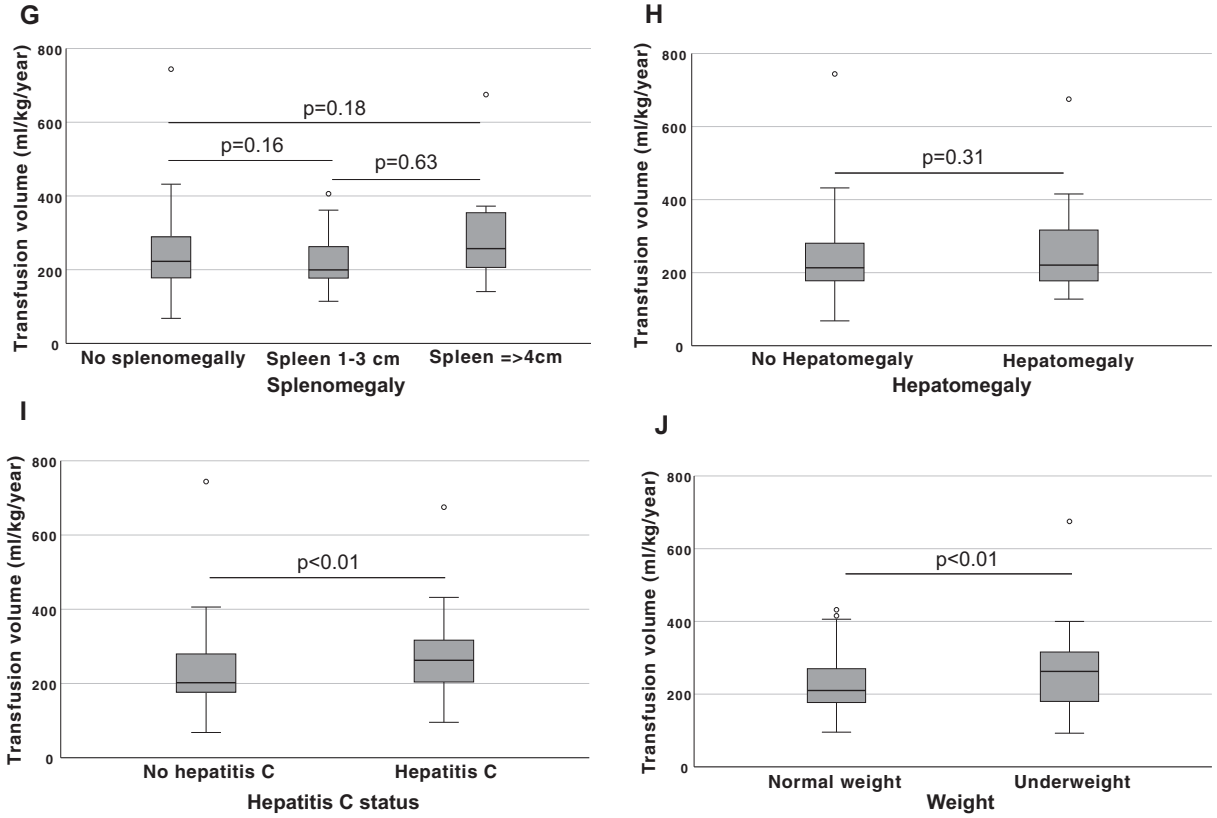

FIGURE 1 Continued

TABLE 2 Adequacy of transfusions in patients with β-thalassemia major and HbE β-thalassemia

Characteristic	β-Thalassemia major ($n = 272$)	HbE β-thalassemia ($n = 53$)	χ^2 value	*P*
Average pretransfusion hemoglobin				
<7.0 g/dL	21 (7.7%)	26 (49.1%)	61.2	<0.001
<9.0 g/dL	145 (53.3%)	51 (96.2%)	34.1	<0.001
Annual transfusion requirement[a]				
>200 mL/kg/year	148 (58.0%)	24 (47.1%)	2.08	0.14
>300 mL/kg/year	52 (20.4%)	8 (15.7%)	0.59	0.44
Spleen status				
Splenomegaly	73 (26.8%)	36 (67.9%)	33.5	<0.001
Splenomegaly of ≥4 cm	6 (2.2%)	6 (11.3%)	10.3	<0.01
Splenectomized	6 (2.2%)	1 (1.9%)	0.02	0.88
Liver status				
Hepatomegaly	73 (26.8%)	31 (58.5%)	20.4	<0.001
Hepatomegaly ≥3 cm	12 (4.4%)	7 (13.2%)	6.23	<0.05
Underweight[b]	80 (32.7%)	16 (34.8%)	0.07	0.77
Short stature[c]	106 (43.1%)	22 (46.8%)	0.222	0.63

Missing data: [a]19 subjects; [b]34 subjects; [c]32 subjects.

of collection, storage conditions, and hematocrit of packed red blood cells need to be considered and studied.[24]

Another important observation of our study is the significant differences observed among patients with β-thalassemia major and HbE β-thalassemia. HbE β-thalassemia is generally considered as a milder disease than β-thalassemia major and patients are expected to have less severe phenotypes.[10,25] However, our findings contradict this belief, and patients with HbE β-thalassemia were having significantly lower pretransfusion hemoglobin levels and higher rates of organomegaly compared with patients with β-thalassemia major. This was despite receiving high transfusion volumes in a large proportion of patients. We believe that this irony could possibly be due to lack of

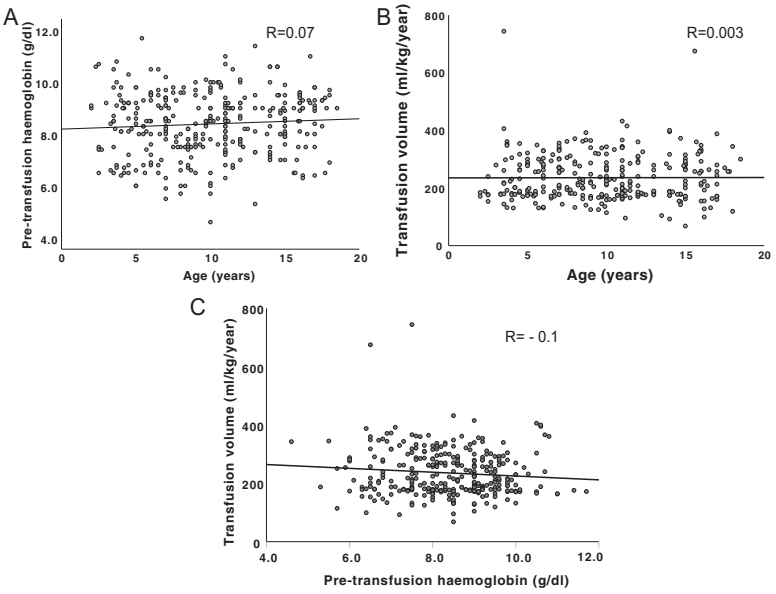

FIGURE 2 Scatter plots demonstrating distribution of (A) mean pretransfusion hemoglobin levels with age, (B) annual transfusion requirements with age, and (C) annual transfusion requirements with pretransfusion hemoglobin levels

TABLE 3 Sociodemographic factors determining optimal blood transfusion status

Parameter		*N*	Number (%) of patients with optimal blood transfusion status	Adjusted odds ratio	*P*
Sex	Male	153	60 (39.2%)	1.03 (0.65–1.61)	0.89
	Female	175	69 (39.4%)		
Maternal education level	Higher education	104	40 (38.5%)	0.85 (0.50–1.43)	0.54
	Primary/ secondary education	224	89 (39.7%)		
Social class by paternal occupation	High (skilled or professional)	105	48 (45.7%)	1.78 (1.01–3.18)	<0.05
	Low (unskilled)	223	81 (36.3%)		
Family income[a]	>LKR 25 000	110	43 (39.1%)	0.78 (0.44–1.38)	0.40
		217	85 (39.2%)		
Hospital stay	1 day	60	22 (36.7%)	0.80 (0.44–1.46)	0.47
	>1 day	268	107 (39.9%)		

[a]Data missing in one subject.

uniform guidelines on blood transfusion therapy for patients with HbE β-thalassemia whose management varied between centers.[26] Therefore, it is timely that specific guidelines are developed to guide blood transfusion therapy for patients with HbE β-thalassemia.

Another important, albeit worrying, finding is the high prevalence of hepatitis C infection in our patients. This raises serious concerns over the safety of blood products and reflects limitations of effective screening of blood donors. Our findings also confirm the results of previous studies that demonstrated lower pretransfusion hemoglobin levels among patients with splenomegaly, hepatomegaly, and hepatitis C infection.[27,28] Similarly, we found that patients with hepatitis C infection have larger annual transfusion requirements compared with non-hepatitis C individuals. Although most patients with hepatitis C infection are treated with directly acting antiviral drugs at present, ribavirin, which is known to cause hemolysis, was used in these patients until recently. Therefore, high annual transfusion requirements of these patients may be related to treatment factors rather than to the disease itself.

Another interesting observation of our study is that patients who are underweight have significantly higher annual transfusion requirements compared with normal-weight patients. To our knowledge, this has not been reported before and we hypothesize that this can be due to increased metabolic rate and demand of patients who are underweight. One third of our patients were underweight and over 40% had short stature, which could predominantly be a result of inadequate transfusions. However, multiple other factors that are not discussed in this paper, for example, inadequate chelation and pituitary dysfunction, could also contribute to underweight and short stature. In our study, we did not observe a change in the transfusion requirement with age. This is in contrast to previous studies that have reported decreasing transfusion requirements with aging.[29] However, we studied patients only up to 18 years, and it may be possible that the blood transfusion requirements decline afterward.

In conclusion, we have shown that over 60% of pediatric patients with transfusion-dependent β-thalassemia have lower than recommended hemoglobin levels despite receiving large volumes of blood

transfusion. Patients with regularly transfused HbE β-thalassemia are undertransfused, and it is timely that specific guidelines are developed to guide transfusion therapy in these patients.

CONFLICTS OF INTEREST

All authors declare no competing interests.

ETHICS STATEMENT

Parents of the participants were briefed about the study, and informed written consent from guardians and assent from children over 12 years were obtained before recruiting into the study. Ethical approval was obtained from the Ethics Review Committee of University of Kelaniya, Sri Lanka.

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