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Serum erythropoietin and its determinants and associations in patients with haemoglobin E β-thalassaemia

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Erythropoietin is a hormone that stimulates erythropoiesis. The role of erythropoietin in the pathophysiology of HbE β-thalassaemia, a subtype of thalassaemia, is understudied. Here, we aim to evaluate the determinants and associations of erythropoietin in HbE β-thalassaemia patients. We conducted a cross-sectional study in Thalassaemia Centres of Colombo North Teaching Hospital, Sri Lanka, from September to December 2024. All patients with HbE β-thalassaemia were recruited. Clinical details were collected using an interviewer schedule. Haemoglobin, ferritin and erythropoietin were measured using standard laboratory methods. Serum samples of non-thalassaemia healthy volunteers were used as controls for erythropoietin measurements. Fifty-two patients (male-42.3%; mean age 24.5 ± 13.4 years) were recruited. The mean erythropoietin of HbE β-thalassaemia patients [137 (± 127) mIU/mL] was significantly higher than that of controls [21.2 (± SD16.3) mIU/mL, p < 0.001]. Among HbE β-thalassaemia patients, erythropoietin showed a gradual and significant decline with age (r = − 0.34, p < 0.05) irrespective of the haemoglobin level. Patients who underwent splenectomy had a significantly lower median erythropoietin level compared to those who did not (40 vs. 129 mIU/mL, p < 0.001). Patients with haemolysis and anaemia-related complications, especially gallstones, had significantly lower median erythropoietin level compared to those without (69.2 vs. 125.9 mIU/mL, p = 0.039). Erythropoietin response in HbE β-thalassaemia decreased gradually with age, irrespective of the degree of anaemia. Splenectomised patients had significantly lower erythropoietin levels compared to non-splenectomised patients. Lower erythropoietin level, which could be due to age-related decline or splenectomy, was positively associated with a high prevalence of haemolysis and anaemia-related complications.

Keywords Haemoglobin E β-thalassaemia, Thalassaemia, Erythropoietin, Splenectomy, Gallstones

Abbreviation

HbE Haemoglobin E

Haemoglobin E (HbE) β-thalassaemia is one of the most prevalent subtypes of β-thalassaemia in the world[1]. Higher prevalences are reported in countries in South and Southeast Asia, including Sri Lanka[2]. HbE β-thalassaemia is due to compound heterozygous inheritance of the β-thalassaemia mutation from one parent and the HbE mutation from the other[3]. The affected individuals demonstrate remarkable clinical heterogeneity, varying from mild anaemia not requiring transfusion to severe transfusion-dependent anaemia[4].

Erythropoietin is an essential hormone that stimulates human erythropoiesis[5]. Due to chronic anaemia, serum erythropoietin levels are markedly elevated in all forms of thalassaemia[6]. In the past, many studies have evaluated the usefulness of serum erythropoietin as a marker of disease severity in thalassaemia. These studies have consistently related higher erythropoietin levels to higher degrees of ineffective erythropoiesis and severe disease phenotypes[7].

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Contrarily, recent clinical studies have shown beneficial effects of erythropoietin in β-thalassaemia[8]. Erythropoietin increases the production of fetal haemoglobin and has antioxidant properties, which are beneficial for patients with β-thalassaemia[9,10]. Several clinical trials have shown some benefit of human recombinant erythropoietin as an adjunct treatment for β-thalassaemia[11,12]. However, evidence about whether recombinant erythropoietin should be recommended for routine use in all patients is still inconclusive.

Despite research for several decades, the role of erythropoietin in the disease pathophysiology of β-thalassaemia is unclear. Specifically, the role of erythropoietin in HbE β-thalassaemia is understudied. Therefore, in this study, we aim to evaluate the determinants and associations of erythropoietin in patients with HbE β-thalassaemia.

Methods

We conducted a cross-sectional study in Adult, Adolescent and Paediatric Thalassaemia Centres of Colombo North Teaching Hospital, Ragama, Sri Lanka, from 01 September to 31 December 2024. All patients with HbE β-thalassaemia attending the hospital for routine clinic follow-up and blood transfusions were recruited consecutively for the study. The diagnosis of HbE β-thalassaemia was confirmed by haemoglobin high-performance liquid chromatography showing haemoglobin F > 50% and haemoglobin E > 30% before commencement of transfusions.

Data were collected using an interviewer schedule, which involved interviewing patients and perusing clinical records. Basic demographic and clinical details including age, gender, age at diagnosis, transfusion frequency, number of blood transfusions, splenectomy status, pretransfusion haemoglobin, ferritin level, complications and hydroxyurea treatment were obtained. Haemoglobin and ferritin were measured as part of the routine management of patients. Two millilitres of additional blood samples were collected for serum erythropoietin measurements. Haemoglobin was measured in complete blood count using the electrical impedance method (Coulter counter). Serum ferritin was measured using a two-site immunoenzymometric assay by VITROS 5600 chemical analyser in a clinically accredited laboratory. Serum erythropoietin was measured using a commercially available enzyme-linked immunosorbent assay kit according to the manufacturer's instructions. Serum samples of 18 non-thalassaemia healthy volunteers (nine males and nine females) were used as controls for erythropoietin measurements.

Data were analysed using IBM SPSS Statistics 30.0. Categorical variables were presented as frequency with percentages, and continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR). Median erythropoietin levels of different categories of HbE β-thalassaemia patients were compared using the Mann–Whitney U test. We defined erythropoietin levels higher than three times the upper normal limit (i.e. > 95.7 mIU/mL) as very high erythropoietin levels for this study. Univariable analysis was performed using the χ^2-test to identify the determinants of very high erythropoietin levels. Multivariable analysis used logistic regression to identify independent determinants of very high erythropoietin levels. Gender, age, age at diagnosis, number of transfusions, transfusion dependency status, pre-transfusion haemoglobin, splenectomy status, hydroxyurea treatment, and serum ferritin were included in the logistic regression model evaluating for determinants of very high erythropoietin. The cut-off for statistical significance was set at $p < 0.05$.

All methods were performed in accordance with the relevant guidelines, regulations and the Declaration of Helsinki. Informed written consent was obtained from all participants or parents (if the participant was < 18 years of age) before recruitment into the study. In children between 12 to 18 years, assent was obtained from the child in addition to the consent from parents. Ethical approval for the study was obtained from the Ethics Review Committee of the Sri Lanka College of Paediatricians (Reference number: SLCP/ERC/2024/17).

Results

We recruited 52 patients with HbE β-thalassaemia for the study.

Demographic and clinical characteristics of the study population

The mean age of the study population was 24.5 (SD ± 13.4) years, and 22 (42.3%) were males. A majority (32, 61.5%) had transfusion dependent thalassaemia, while 20 (38.5%) had non-transfusion dependent thalassaemia. Sixteen (30.8%) patients underwent splenectomy at a mean age of 16.0 (SD ± 8.2) years (range: 22 months–35 years). The demographic and clinical characteristics of the study population are shown in Table 1.

Serum erythropoietin levels in HbE β-thalassaemia patients

The mean serum erythropoietin level of HbE β-thalassaemia patients was 137 (± SD127) mIU/mL. It was significantly higher than the mean erythropoietin level of controls [21.2 (± SD16.3) mIU/mL, $p < 0.001$]. This difference was consistently observed in males and females (Fig. 1). Forty-three (82.7%) HbE β-thalassaemia patients had serum erythropoietin above the reference range of 31.9 mIU/mL, while 29 (55.7%) had very high erythropoietin levels three times above the upper normal range.

Age-related changes in erythropoietin levels in HbE β-thalassaemia patients

Serum erythropoietin levels were significantly higher among children less than 18 years (median: 127mIU/mL; IQR: 106–262) compared to adults (median: 71mIU/mL; IQR: 32–156), ($p = 0.020$). Serum erythropoietin showed a gradual and significant decline with age ($r = -0.34$, $p < 0.05$) (Fig. 2). The decrease was consistently observed in males and females and those with baseline haemoglobin < 7 g/dL and > = 7 g/dL.

Characteristic	Frequency (n = 52)	Percentage (%)
Gender		
Male	22	42.3
Female	30	57.7
Age group		
≤ 5 years	5	9.6
6–18 years	12	23.1
19–35 years	20	38.5
36–50 years	14	26.9
> 50 years	1	1.9
Age at diagnosis		
< 2 years	20	38.5
2–4 years	11	21.2
5–12 years	16	30.8
> 12 years	5	9.6
Number of lifetime transfusions		
0	2	3.8
1–10	8	15.4
11–100	5	9.6
> 100	37	71.2
Transfusion dependency		
Transfusion dependent thalassaemia	32	61.5
Non-transfusion dependent thalassaemia	20	38.5
Baseline pre-transfusion haemoglobin		
< 6.0 g/dL	10	19.2
6.0–6.9 g/dL	19	36.5
7.0–7.9 g/dL	15	28.8
8.0–8.9 g/dL	6	11.5
> 9.0 g/dL	2	3.8
Splenectomised or not		
Splenectomised	16	30.8
Not splenectomised	36	69.2
Hydroxyurea treatment		
Currently taking	13	25.0
Taken and stopped	19	36.5
Never taken	20	38.5
Iron chelation		
Currently taking	41	78.8
Not taking	11	21.2
Serum ferritin		
< 1000 ng/mL	20	38.5
1000–2499 ng/mL	21	40.4
> = 2500 ng/mL	11	21.2
Anaemia-related complications		
Gallstones	20	38.5
Leg ulcers	12	23.1
Fractures	5	9.6
Pulmonary hypertension	2	3.8

Table 1. Demographic and clinical characteristics of HbE β-thalassaemia patients.

Associations between clinical characteristics and erythropoietin levels among HbE β-thalassaemia patients

Higher erythropoietin levels were found among patients diagnosed before 4 years (median: 125mIU/mL; IQR: 70–219) compared to those who were diagnosed after 4 years (median: 42mIU/mL; IQR: 24–141) ($p = 0.013$). Patients who had undergone splenectomy (median: 40mIU/mL; IQR 16–93) had significantly lower erythropoietin levels compared to non-splenectomised patients (median: 129mIU/mL; IQR: 65–220) ($p < 0.001$). Additionally, median erythropoietin levels were higher in males (128 mIU/mL), those who had < 100 transfusions (125 mIU/

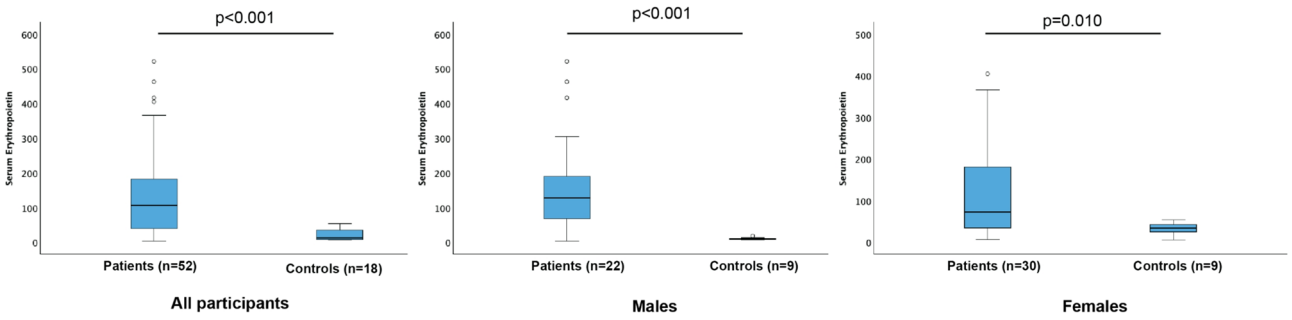

Fig. 1. Serum erythropoietin levels of HbE β-thalassaemia patients and controls.

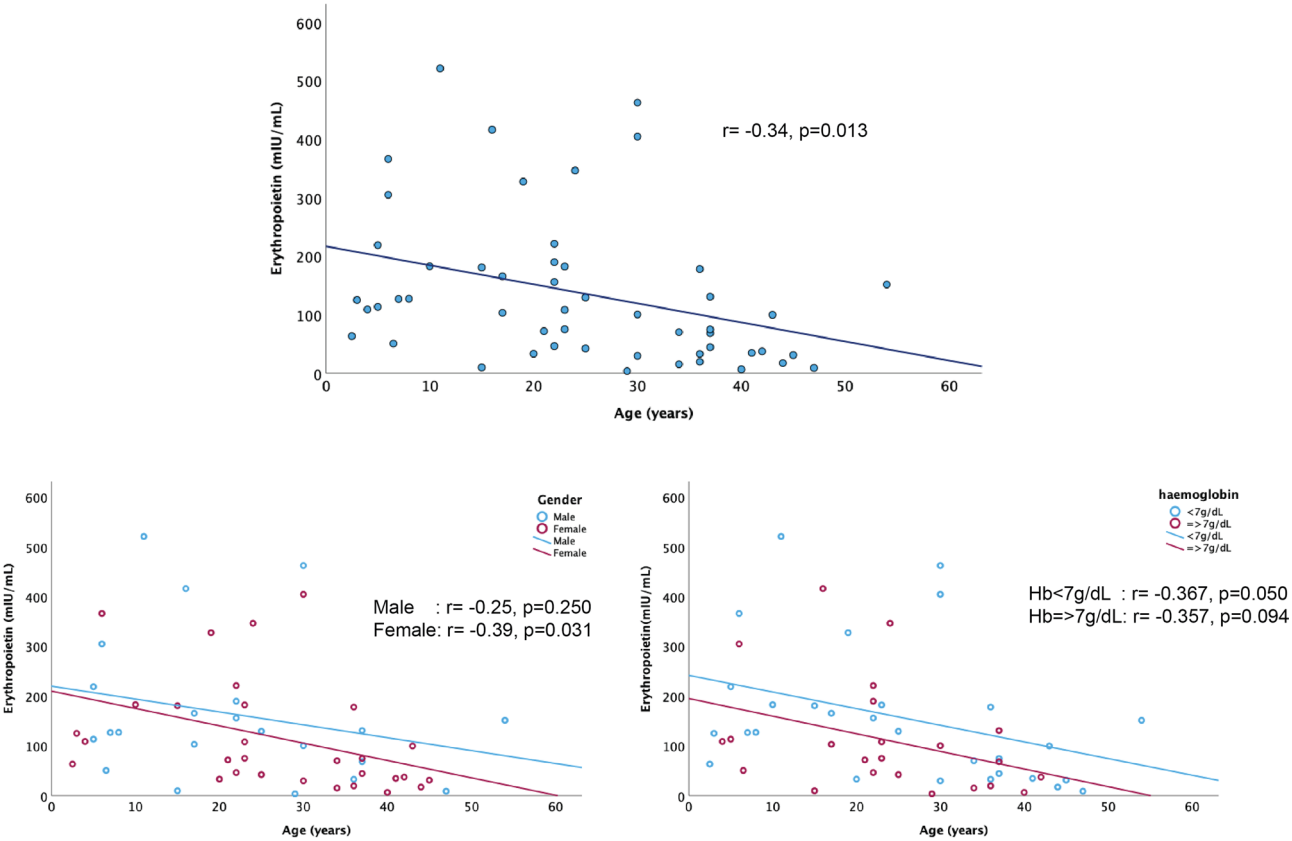

Fig. 2. Serum erythropoietin levels of HbE β-thalassaemia patients and controls.

mL) and patients with pretransfusion haemoglobin < 7 g/dL (127 mIU/mL) compared to females (73 mIU/mL), those who had > 100 transfusions (75 mIU/mL) and patients with pretransfusion haemoglobin > 7 g/dL (75 mIU/mL), respectively. However, these differences were not statistically significant. Erythropoietin levels were not significantly different between transfusion-dependent and non-transfusion-dependent patient groups (Fig. 3).

Determinants of very high erythropoietin levels in HbE β-thalassaemia

Erythropoietin level above three times the upper normal limit (i.e. > 95.7 mIU/mL) was defined as very high levels. Univariable analysis revealed that significantly higher proportions of males compared to females (OR = 3.48, p = 0.035), children compared to adults (OR = 6.22, p = 0.007), age at diagnosis < 4 years compared to > 4 years (OR = 3.41, p = 0.035) and non-splenectomised compared to splenectomised (OR = 6.81, p = 0.003) had very high erythropoietin levels (Table 2). However, multivariable analysis using logistic regression revealed that only non-splenectomy (p = 0.013) was an independent factor associated with very high erythropoietin levels.

Associations between HbE β-thalassaemia complications and erythropoietin levels

Next, we analysed the erythropoietin levels in patients with or without complications (Fig. 4). Erythropoietin levels were significantly lower among patients with gallstones (median: 69.2mIU/mL; IQR: 22.3–149.3)

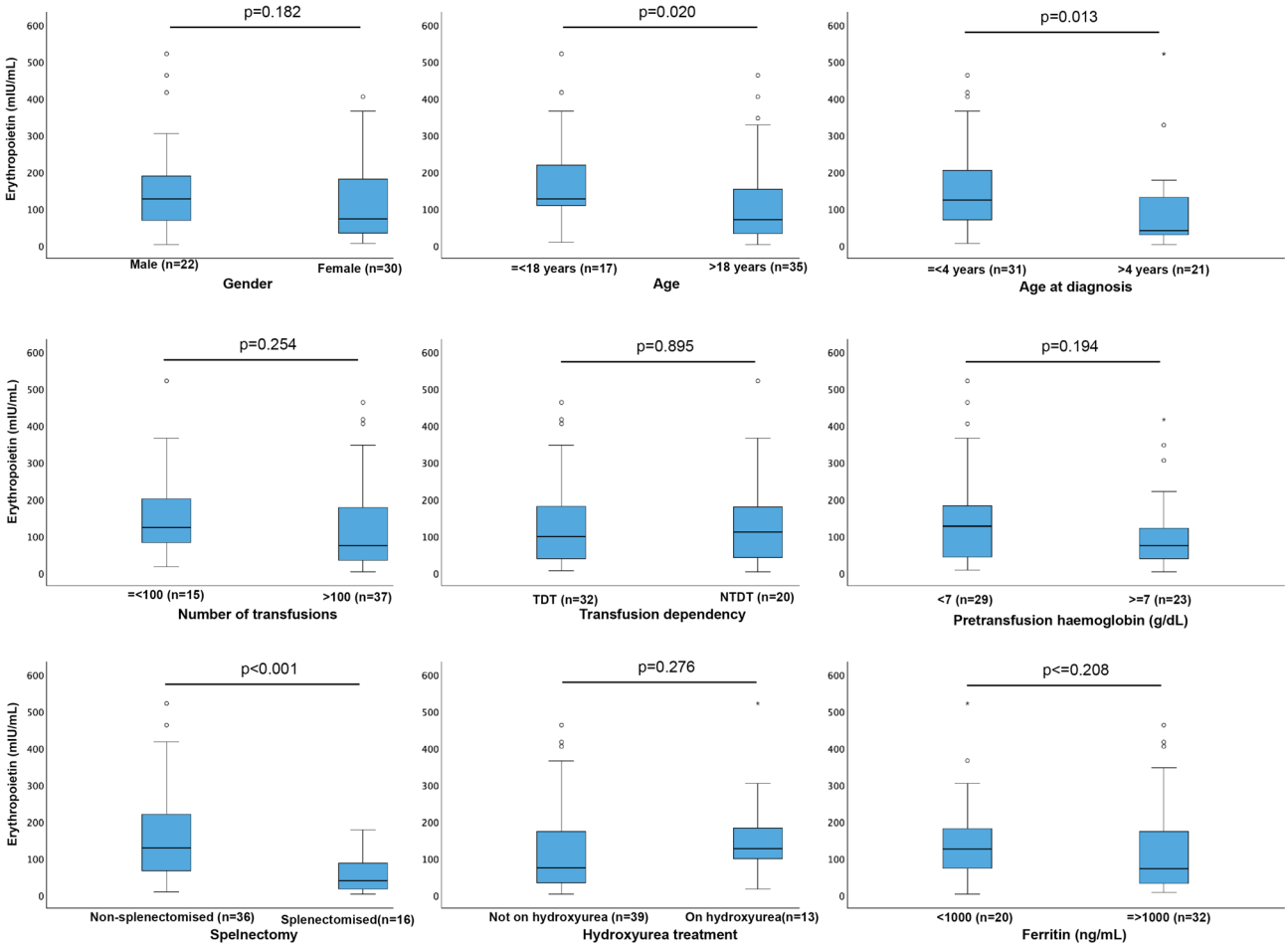

Fig. 3. Serum erythropoietin levels of different clinical categories of HBE β-thalassaemia patients.

compared to those without (median: 125.9mIU/mL; IQR: 53.7–210.0), (p = 0.039). Patients with leg ulcers had lower erythropoietin levels (median: 72.4mIU/mL; IQR: 17.7–122.1) compared to those without (median: 119.3mIU/mL; IQR: 42.7–210.0), although the difference was not significant (p = 0.082). Similarly, median erythropoietin levels were lower in patients who had fractures (99.7 vs. 108.9), echocardiography evidence of cardiomyopathy (54.6 vs. 108.5) and pulmonary hypertension (93.4 vs. 105.7) compared to those who did not have the complications; nonetheless, the differences were not statistically significant.

Discussion

In this study, we examined the erythropoietin levels in patients with HbE β-thalassaemia to understand the clinical and pathophysiological significance of erythropoietin in thalassaemia. Our study confirmed that HbE β-thalassaemia patients have very high erythropoietin levels, which could sometimes be over 10 times the upper normal limits. This agrees with the previous findings that reported high erythropoietin levels in different types of thalassaemia[13–15].

Our study revealed that the serum erythropoietin gradually decreased with increasing age among HbE β-thalassaemia patients of both genders. The comparable declines were observed in patients with lower (< 7 g/dL) and higher (> = 7 g/dL) haemoglobin levels, demonstrating that the age-related decline of erythropoietin is independent of the degree of anaemia. This contrasts with the findings of studies involving healthy, non-anaemic populations, which have shown no change or a rising trend in erythropoietin with age[16–18]. However, previous studies among patients with thalassaemia have concluded that erythropoietin levels as well as erythropoietin response to anaemia decrease with age[2,19]. Although the exact mechanism of this paradoxical response in β-thalassaemia is not fully understood, the presence of supra-physiological levels of erythropoietin throughout life, chronic inflammation, iron overload, and age-related decline in renal function are potential pathophysiological mechanisms.

Another finding of the study was that higher erythropoietin levels were positively associated with features indicating severe disease. Patients who were diagnosed early in life (before 4 years) and those who had a lower baseline haemoglobin level (< 7 g/dL) had higher erythropoietin levels. This will most likely be due to an increased rate of ineffective erythropoiesis in patients with severe disease.

Characteristic	Number (%) with very high EPO level	Unadjusted odds ratio (OR), 95%CI, and p-value	Adjusted odds ratio (AOR), 95%CI, and p-value
Gender			
Male (n = 22)	16 (72.7%)	OR = 3.48 95%CI = 1.07–11.3 p = 0.035	AOR = 6.911 95%CI = 0.90–52.7 p = 0.062
Female (n = 30)	13 (43.3%)		
Age category			
Children (n = 17)	14 (82.4%)	OR = 6.22 95%CI = 1.51–25.6 p = 0.007	AOR = 0.75 95%CI = 0.03–20.0 p = 0.868
Adults (n = 35)	15 (42.9%)		
Age at diagnosis			
= < 4 years (n = 31)	21 (67.7%)	OR = 3.41 95%CI = 1.07–10.8 p = 0.035	AOR = 5.10 95%CI = 0.77–33.6 p = 0.090
> 4 years (n = 21)	8 (38.1%)		
No. of transfusions			
< 100 (n = 15)	11 (73.3%)	OR = 2.90 95%CI = 0.78–10.7 p = 0.104	AOR = 1.22 95%CI = 0.03–42.0 p = 0.909
> 100 (n = 37)	18 (48.6%)		
Transfusion dependency			
Transfusion dependent (n = 32)	17 (53.1%)	OR = 0.75 95%CI = 0.24–2.34 p = 0.627	AOR = 7.41 95%CI = 0.29–185.6 p = 0.223
Non-transfusion dependent (n = 20)	12 (60.0%)		
Pre-transfusion haemoglobin			
< 7 g/dL (n = 29)	18 (62.1%)	OR = 1.78 95%CI = 0.58–5.41 p = 0.304	AOR = 4.00 95%CI = 0.72–22.0 p = 0.111
> = 7 g/dL (n = 23)	11 (47.8%)		
Splenectomy			
Non-splenectomy (n = 36)	25 (69.4%)	OR = 6.81 95%CI = 1.79–25.9 p = 0.003	AOR = 15.9 95%CI = 1.80–140.9 p = 0.013
Splenectomised (n = 16)	4 (25.0%)		
Hydroxyurea treatment			
On hydroxyurea (n = 13)	10 (76.9%)	OR = 3.50 95%CI 0.83–14.73 p = 0.076	AOR = 6.35 95%CI = 0.73–54.9 p = 0.093
Not on hydroxyurea (n = 39)	19 (48.7%)		
Ferritin			
< 1000 ng/mL (n = 20)	14 (70.0%)	OR = 2.64 95%CI = 0.81–8.62 p = 0.102	AOR = 4.61 95%CI = 0.42–50.3 p = 0.210
> = 1000 ng/mL (n = 32)	15 (46.9%)		

Table 2. Determinants of very high erythropoietin levels. *EPO, erythropoietin; OR, Odds ratio; AOR, Adjusted odds ratio; CI, confidence interval.

The study revealed contrasting observations regarding complications of HbE β-thalassaemia. We observed lower erythropoietin levels in patients who developed haemolysis- and anaemia-related complications of thalassaemia, such as gallstones, leg ulcers, fractures and pulmonary hypertension. The reason for this association is unclear; however, this finding supports the attempts to use recombinant erythropoietin as an adjunct treatment for β-thalassaemia. A recent clinical trial reported the clinical superiority of combined hydroxyurea with recombinant human erythropoietin over hydroxyurea alone in β-thalassemia[11]. Overall, it appears that erythropoietin is protective against anaemia-related complications in HbE β-thalassaemia.

Another important finding of the study is the observation of significantly lower erythropoietin levels among splenectomised patients. The spleen is an important site of red blood cell destruction; therefore, removing the spleen leads to improvement in haemoglobin and anaemia, which could decrease the renal production of erythropoietin[20]. Similarly, there could be changes in the physiology of how the body senses hypoxia and makes red blood cells in the absence of a spleen. Nonetheless, the exact reason behind the association of low erythropoietin in splenectomised patients is not fully understood and requires further research.

Splenectomy used to be a routine therapeutic procedure that improved haemoglobin in HbE β-thalassaemia a decade ago; however, it is less often performed nowadays[21]. This is due to the high prevalence of long-term complications that include pulmonary hypertension, leg ulcers and thromboembolism in splenectomised patients[22,23]. The exact pathophysiology for the higher prevalence of complications is unclear. Our findings of significantly lower erythropoietin levels in splenectomised patients and the association between low erythropoietin and anaemia-related complications indicate that low erythropoietin following splenectomy could play a role in the pathophysiology of post-splenectomy complications of thalassaemia.

We also observed higher erythropoietin levels in patients treated with hydroxyurea. Hydroxyurea is an antimetabolite drug used as an adjunct therapy for β-thalassaemia primarily by inducing fetal haemoglobin[24]. Hydroxyurea inhibits ineffective erythropoiesis; however, it induces stress erythropoiesis by cell stress signalling, which releases erythroid progenitors containing high fetal haemoglobin[25,26]. The beneficial effects of hydroxyurea

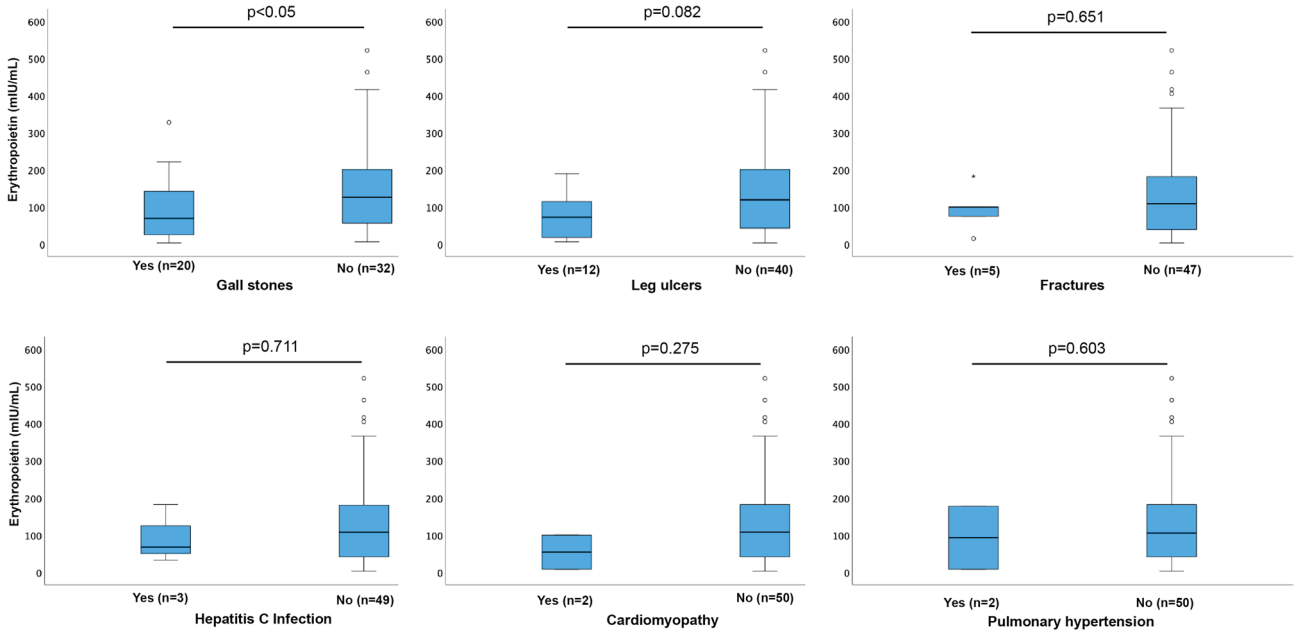

Fig. 4. Serum erythropoietin levels of patients with or without complications of HBE β-thalassaemia.

in β-thalassaemia could probably be mediated through or associated with high erythropoietin levels; however, further validation of this fact is required.

One limitation of the study is that we were able to evaluate the effects of only a few variables as determinants of very high erythropoietin levels. Our analysis included several factors related to β-thalassaemia (gender, age, age at diagnosis, number of transfusions, transfusion dependency status, pre-transfusion haemoglobin, splenectomy status, hydroxyurea treatment, and serum ferritin) as co-factors but did not include other non-thalassaemia related confounders such as renal function, inflammatory markers, and hormonal levels.

Another limitation is that we could not fully elucidate the effect of ageing on the causation of anaemia-related complications such as gallstones, leg ulcers, and pulmonary hypertension. We observed an age-related decline in erythropoietin levels and an association between low erythropoietin levels and a higher prevalence of anaemia-related complications. Although the higher prevalence of anaemia-related complications such as gallstones, leg ulcers, and pulmonary hypertension in older patients may be attributed to the age-related decline in erythropoietin, such assumptions require backing from regression analysis to eliminate the confounding effects of ageing. However, the patient numbers in each complication category were too low for us to perform meaningful regression analysis.

In this paper, we described an in-depth evaluation of the determinants, effects and role of erythropoietin in patients with HbE β-thalassaemia. We conclude that erythropoietin levels among HbE β-thalassaemia patients are significantly higher than in normal individuals, and higher levels reflect severe disease with earlier onset and low baseline haemoglobin. Erythropoietin response in HbE β-thalassaemia decreases gradually with age, irrespective of the degree of anaemia. Splenectomised patients had significantly lower erythropoietin levels compared to non-splenectomised patients. Lower erythropoietin levels, which could be due to age-related decline or splenectomy, are positively associated with a high incidence of haemolysis or anaemia-related complications.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

DA, SP, AP and SM conceptualised the study. DA and SM performed the literature review. DA and SM wrote the proposal and obtained ethical approval. DA, SP, AP and SM were involved in data collection. DA and SM analysed data. DA, AP and SM wrote the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

Ethical approval for the study was obtained from the Ethics Review Committee of the Sri Lanka College of Paediatricians (Reference number: SLCP/ERC/2024/17). Informed consent was obtained from all study participants before recruitment.

Additional information

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