ORIGINAL ARTICLE

# Cutaneous Manifestations in Adult Thalassemia Patients

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**Background**: A wide range of cutaneous manifestations have been described in thalassemia patients. No studies have been conducted in Southeast Asia where there is a high prevalence of hemoglobin E (Hb E) thalassemia.

**Objective**: The primary objectives of the present study were to determine the prevalence of cutaneous manifestations among adult thalassemia patients and assess how cutaneous findings differ between patients with and without β-thalassemia (β-thal)/Hb E. Secondary objectives were to determine any associations between cutaneous manifestations and clinical or laboratory findings and to evaluate quality of life (QoL).

**Materials and Methods**: The present study was a cross-sectional descriptive study conducted between April 2021 and December 2022 in Thailand. Adults aged 18 years and older with any type of thalassemia were eligible. The authors collected relevant demographic data, cutaneous and laboratory findings, as well as responses to a validated Thai version of the Dermatology Life Quality Index (DLQI).

**Results**: One hundred patients (37% male) were included, with a median age of 33 (IQR of 24, 41) years. Of these, 76% had β-thal/Hb E. Xerosis was the most common cutaneous manifestation at 69%. Hyperpigmentation was more common in patients with β-thal/Hb E than those without at 41% versus 17% (p=0.031). Extramedullary erythropoiesis, xerosis, and serum ferritin were significantly associated with hyperpigmentation. The overall median DLQI score was 0 (IQR 0, 2).

**Conclusion**: Xerosis was the most common cutaneous findings in adult thalassemia patients, and hyperpigmentation was more common in patients with β-thal/Hb E. However, cutaneous changes had low impact on patients' QoL.

**Keywords**: Thalassemia; Cutaneous manifestations; Hemoglobin E thalassemia

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Thalassemia is one of the most common inherited anemias worldwide, especially in the Mediterranean, African, and Southeast Asian countries[1]. In patients with thalassemia, abnormal hemoglobin formation leads to ineffective erythropoiesis and hemolysis, which in turn, results in anemia[2]. Thalassemia can be either 1) transfusion-dependent (TDT), such as homozygous β°-thalassemia or β-thalassemia/hemoglobin E (β-thal/Hb E), or 2) non-transfusion-dependent (NTDT), such as hemoglobin H disease and some cases of β-thal/Hb E[3]. In addition to anemia, thalassemia can result in multi-system complications including pulmonary hypertension, heart failure, diabetes mellitus, extramedullary hematopoiesis, gallstones, hypothyroidism, osteoporosis, thrombosis, infection, and leg ulcers[3]. The literature describes various cutaneous manifestations of the disease, including xerosis, pruritus, idiopathic guttate hypomelanosis, urticaria, ephelides, scarring, tinea, and injection-site reactions to iron chelator[4-10].

Studies of such cutaneous manifestations have been conducted in Egypt, Turkey, Iraq, and India[4-10]. However, most have focused on children with β-thal major and, to the best of our knowledge, there has yet been no study conducted in Southeast Asia, which has a high prevalence of Hb E thalassemia[11]. The authors determined to study the prevalence of cutaneous manifestations among adult thalassemia patients and compared cutaneous manifestations in adult patients with and without β-thal/Hb E. Additionally, the present study aimed to determine their potential association of cutaneous manifestations with clinical or laboratory findings and to evaluate dermatology-specific health-related quality of life (QoL) in these patients.

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## Materials and Methods

The present study was a cross-sectional descriptive study conducted between April 2021 and December 2022 at a blood transfusion clinic in Thailand. It was approved by the University Ethics Committee for Human Research (HE631085), and written informed consent was obtained from all participants before enrollment. Adults aged 18 years or older with any type of thalassemia were eligible for enrollment. Those with psychiatric disorders or unable to read and write in Thai were excluded. The authors collected relevant demographic, clinical, and laboratory data including age, gender, underlying diseases, current medications, type of thalassemia, and history of splenectomy and thalassemia complications, as well as, complete blood count, serum ferritin, renal and liver function, chest radiography, electrocardiography, cardiac T2* magnetic resonance imaging, and bone densitometry results. The authors used five-year mean serum ferritin to represent serum ferritin, while previous studies had commonly used the most recent results. All patients were examined by a dermatologist (NJ), who recorded their Fitzpatrick skin type and any cutaneous findings. Pruritus was assessed by using visual analog scale (VAS), ranging from 0 for no pruritus to 10 for very severe pruritus. Dermatology-specific health-related QoL was evaluated by using the validated Thai version of the Dermatology Life Quality Index (DLQI)[12], a self-administered questionnaire consisting of ten questions in six domains as symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Total scores can range from 0 for no effect on QoL at all to 30 for extremely large effect[13]. All patients were asked about their habits regarding skin care, focusing on moisturizer usage, and warm bathing. Skin conditions were diagnosed based on relevant clinical and/or histopathological results.

### Sample size calculation

The authors used the formula below to estimate the infinite population proportion:

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

where n was the sample size, Z was 1.959964 at 0.05 level of significance, p was the proportion of xerosis in thalassemia patients from a previous study (0.72), and d was the estimated 9% rate of error[6]. Based on this calculation a sample size of at least 96 was required.

### Statistical analysis

Statistical analysis was carried out using R version 4.1.2[14]. Descriptive statistics were presented as mean with standard deviation (SD) for normally distributed continuous data, median with interquartile range (IQR) for non-normally distributed continuous data, and percentage for categorical data. The authors used an independent t-test or Wilcoxon rank sum test for continuous data or a chi-squared test for categorical data, to determine the association between laboratory findings and cutaneous manifestations based on continuous data. The authors also performed multiple logistic regression analysis to determine any associations between findings of clinical and laboratory, and cutaneous manifestations. Factors with a p-value less than 0.2 according to univariate analysis, as well as certain factors reported in the literature to be related, were subjected to multivariate analysis. Backward elimination with Akaike information criteria was used to generate the final model. The p-values of less than 0.05 were considered statistically significant.

## Results

One hundred thalassemia patients were included in the present study, 37% were male, with a median age of 33 with an IQR of 21 and 41 years. Seventy-six patients (76%) had β-thal/Hb E, while the remaining 10% had EA Bart's disease, 6% had Hb H with Hb CS, 4% had EA Bart's with Hb CS, and 4% had Hb H disease, which were classified as alpha thalassemia with or without Hb E. Forty percent of patients underwent splenectomy, and iron chelators were used in 95%. The most common chelator was deferiprone in 63%, and some patients received a combination of iron chelators. Liver iron overload was the most common complication in 80%. Table 1 presents a comparison of demographic data and laboratory findings between β-thal/Hb E and non-β-thal/Hb E patients[15-18]. The authors found significant intergroup differences in the rates of splenectomy and extramedullary hematopoiesis complications, as well as in white blood cell and platelet count.

The most common Fitzpatrick skin type in thalassemia patients was type 3 in 60%, followed by type 4 and type 5, in 38% and 2%, respectively. The most common cutaneous manifestations in this group were xerosis at 69%, followed by lentigines, scar, hyperpigmentation, and eczema at 54%, 41%, 35%, and 25%, respectively. The degree of xerosis varied among patients (Figure 1). Only 13% of patients had pruritus without skin lesions, with a median VAS

**Table 1.** Comparison of baseline characteristics and laboratory findings in β-thal/Hb E and non-β-thal/Hb E patients

| Characteristics | All patients (n=100) | β-thal/Hb E (n=76) | Non-β-thal/Hb E (n=24) | p-value |
|---|---|---|---|---|
| Age (years); median (IQR) | 33 (24, 41) | 33 (25, 39) | 34 (21, 47) | >0.9 |
| Male; n (%) | 37 (37) | 31 (41) | 6 (25) | 0.2 |
| Underlying conditions; n (%) | | | | |
| DM | 6 (6) | 5 (7) | 1 (4) | >0.9 |
| Thyroid disorder | 9 (9) | 7 (9) | 2 (8) | >0.9 |
| HCV infection | 10 (10) | 9 (12) | 1 (4) | 0.4 |
| Splenectomy; n (%) | 40 (40) | 37 (49) | 3 (12) | 0.002 |
| Use of iron chelator; n (%) | 95 (95) | 74 (97) | 21 (88) | 0.088 |
| Deferiprone | 63 (63) | 46 (61) | 17 (71) | 0.4 |
| Deferasirox | 24 (24) | 21 (28) | 3 (12) | 0.13 |
| Deferoxamine | 20 (20) | 16 (21) | 4 (17) | 0.8 |
| Thalassemia complications; n (%) | | | | |
| Liver iron overload* | 80 (80) | 63 (83) | 17 (71) | 0.2 |
| Gallstone | 57 (57) | 47 (62) | 10 (42) | 0.082 |
| Extramedullary hematopoiesis | 36 (36) | 34 (45) | 2 (8) | 0.001 |
| Osteoporosis | 35 (35) | 30 (39) | 5 (21) | 0.10 |
| Pulmonary hypertension** | 17 (17) | 15 (20) | 2 (8) | 0.3 |
| Pancreatic diabetes mellitus | 4 (4) | 4 (5) | 0 (0) | 0.6 |
| Cardiac hemochromatosis*** | 3 (3) | 2 (3) | 1 (4) | 0.6 |
| Hemoglobin (g/dL); median (IQR) | 7.60 (6.80, 8.12) | 7.55 (6.77, 8.20) | 7.70 (6.90, 7.90) | 0.5 |
| White blood cell count (cells/$mm^3$); median (IQR) | 8,110 (5,992, 10,575) | 8,832 (6,749, 11,555) | 6,465 (5,508, 7,735) | 0.001 |
| Platelet count (/$mm^3$); median (IQR) | 255,500 (187,500, 625,250) | 346,500 (199,750, 658,000) | 230,500 (173,750, 248,750) | 0.012 |
| Creatinine (mg/dL); median (IQR) | 0.62 (0.50, 0.72) | 0.61 (0.50, 0.71) | 0.63 (0.54, 0.76) | 0.3 |
| ALT (U/L); median (IQR) | 24 (15, 37) | 24 (15, 36) | 20 (15, 42) | 0.5 |
| AST (U/L); median (IQR) | 32 (26, 50) | 31 (26, 44) | 37 (25, 52) | 0.5 |
| Serum ferritin (mcg/L); median (IQR) | 1,410.00 (585, 3,274) | 1,418 (774, 3,117) | 1,364 (627, 2,202) | 0.3 |

β-thal=β-thalassemia; Hb E=hemoglobin E; IQR=interquartile range; DM=diabetes mellitus; HCV=hepatitis C virus; ALT=alanine transferase; AST=aspartate transaminase

* Liver iron overload was defined as liver iron concentration from MRI >2 mg Fe/g dry weight[15], ** Pulmonary hypertension was defined as tricuspid regurgitation velocity >3 m/s from echocardiography or pulmonary artery mean pressure ≥25 mmHg from cardiac catheterization[16,17], *** Cardiac hemochromatosis was defined as cardiac T2* from MRI <20 msec[18]

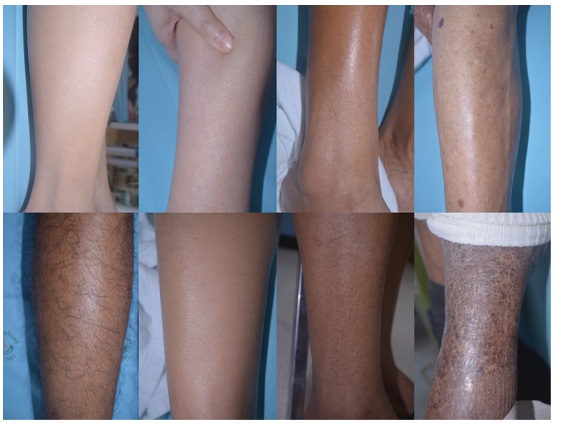

**Figure 1.** Variation of severity in xerosis cutis among patients.

score of 5 (IQR 3, 5). Two percent of the patients had active leg ulcers, and another 14% had a history of leg ulcers. Of the 60 patients who received subcutaneous iron chelators, 20% experienced injection-induced erythema. Pseudoxanthoma elasticum (PXE)-like lesions were found in only one patient who had β-thal/Hb E, but she declined a skin biopsy to confirm the diagnosis (Figure 2). A comparison of other cutaneous findings can be found in Table 2. A significantly higher proportion of patients with β-thal/Hb E exhibited hyperpigmentation at 41% versus 17% (p=0.031). According to univariate analysis (Table 3), only extramedullary erythropoiesis, xerosis, platelet count, creatinine, and serum ferritin were associated with hyperpigmentation (p<0.2). All were subjected to subsequent multivariate analyses. Variables significantly associated with hyperpigmentation according to multiple logistic regression analysis included extramedullary erythropoiesis, xerosis, and serum ferritin (odds ratio [OR] 3.37, 95% confidence

**Table 2.** Comparison of cutaneous manifestations in β-thal/Hb E and non-β-thal/Hb E patients

| Cutaneous manifestations | All patients (n=100); n (%) | β-thal/Hb E (n=76); n (%) | Non-β-thal/HbE (n=24); n (%) | p-value |
|---|---|---|---|---|
| Xerosis | 69 (69) | 54 (71) | 15 (62) | 0.4 |
| Lentigines | 54 (54) | 42 (55) | 12 (50) | 0.7 |
| Scar* | 41 (41) | 31 (41) | 10 (42) | >0.9 |
| Hyperpigmentation** | 35 (35) | 31 (41) | 4 (17) | 0.031 |
| Eczema | 25 (25) | 19 (25) | 6 (25) | >0.9 |
| Prurigo simplex | 11 (11) | 7 (9) | 4 (17) | 0.5 |
| Nonspecific eczema | 9 (9) | 9 (12) | 0 (0) | 0.11 |
| Dyshidrosis | 3 (3) | 2 (3) | 1 (4) | 0.6 |
| Contact dermatitis | 2 (2) | 1 (1) | 1 (4) | 0.4 |
| Idiopathic guttate hypomelanosis | 19 (19) | 13 (17) | 6 (25) | 0.4 |
| Melasma | 17 (17) | 14 (18) | 3 (12) | 0.8 |
| Urticaria | 14 (14) | 11 (14) | 3 (12) | >0.9 |
| Pruritus | 13 (13) | 9 (12) | 4 (17) | 0.5 |
| Acne vulgaris | 12 (12) | 7 (9) | 5 (21) | 0.2 |
| Erythema caused by injection | 12 (20) | 12 (23) | 0 (0) | 0.3 |
| Nail disorders*** | 7 (7) | 6 (8) | 1 (4)** | >0.9 |
| Pityriasis versicolor | 5 (5) | 4 (11) | 1 (9) | >0.9 |
| Alopecia**** | 4 (4) | 4 (5) | 0 (0) | 0.6 |
| Dermatophytosis | 4 (4) | 3 (4) | 1 (4) | >0.9 |
| Active leg ulcers | 2 (2) | 1 (1) | 1 (4) | 0.4 |
| Pseudoxanthoma elasticum-like lesions | 1 (1) | 1 (1) | 0 (0) | >0.9 |

β-thal=β-thalassemia; Hb E=hemoglobin E

* Scars were defined as non-surgical scars observed by the physician, ** Hyperpigmentation was defined as diffuse skin darkening which may be prominent on sun-exposed areas. Diagnosis was made by clinical examination, *** Nail disorders: chronic paronychia (3 cases, some cases had another concomitant abnormal nail findings), white nail (1 case), overcurvature of the nails (1 case), subungual hematoma (1 case), onychotillomania (1 case), onycholysis (1 case), and tinea unguium (1 case), **** Alopecia: telogen effluvium (3 cases) and androgenetic alopecia (1 case)

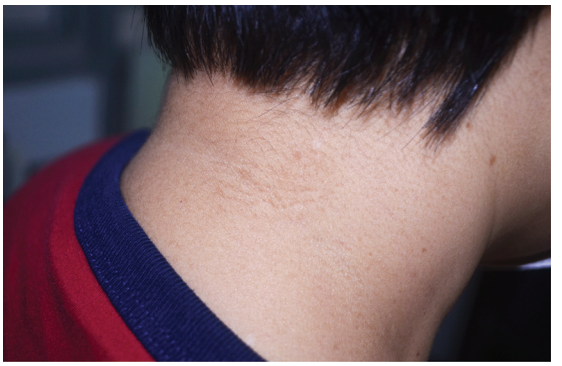

**Figure 2.** Pseudoxanthoma elasticum-like lesions in a β-thal/Hb E patient. The patient had yellow papules-forming plaques in a reticular pattern located on the posterior neck.

interval [CI] 1.12 to 11.15, p=0.04; OR 6.28, 95% CI 1.58 to 34.77, p=0.02; OR 1.00, 95% CI 1.00 to 1.00, p=0.04, respectively) (Table 3).

The median age of patients with pruritus was significantly higher than those without at 42 years versus 31 years (p=0.003). A higher proportion of patients with pruritus also had xerotic skin, but the difference was not statistically significant. Interestingly, a significantly higher proportion of patients with pruritus used moisturizer regularly at 46% versus 14% (p=0.012) (Table 4).

The median DLQI score in thalassemia and β-thal/Hb E patients was 0 (IQR 0, 2 and 0, 1, respectively) and in non-β-thal/Hb E patients was 0.5 (IQR 0, 2). There was no significant difference in DLQI score among groups (p=0.4).

## Discussion

Thalassemia is one of the most common inherited anemias worldwide, especially in Southeast Asia. Most studies have been focused on treatments, complications, and treatment-related complications. Few have investigated cutaneous manifestations, and most of those have only examined children with β-thalassemia major. The aim of the present study was to compare cutaneous manifestations in β-thal/Hb E and non-β-thal/Hb E adults, identify any associations between cutaneous manifestations and clinical or laboratory findings, and evaluate dermatology-specific health-related QoL.

**Table 3.** Factors associated with hyperpigmentation according to multiple logistic regression analysis

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Crude OR | 95% CI | p-value | Adjusted OR | 95% CI | p-value |
| Extramedullary erythropoiesis | 4.17 | 1.67 to 10.91 | <0.01 | 3.37 | 1.12 to 11.15 | 0.04 |
| Xerosis | 3.02 | 1.15 to 8.98 | 0.03 | 6.28 | 1.58 to 34.77 | 0.02 |
| Platelet count | 1.00 | 1.00 to 1.00 | 0.14 | 1.00 | 1.00 to 1.00 | 0.24 |
| Creatinine | 0.07 | 0.00 to 0.75 | 0.05 | 0.02 | 0.00 to 0.72 | 0.05 |
| Serum ferritin | 1.00 | 1.00 to 1.00 | 0.02 | 1.00 | 1.00 to 1.00 | 0.04 |

OR=odds ratio; CI=confidence interval

**Table 4.** Comparison of factors associated with pruritus and no pruritus in thalassemia patients

| Variables | Pruritus (n=13) | No pruritus (n=87) | p-value |
|---|---|---|---|
| Age (years); median (IQR) | 42 (34, 59) | 31 (23, 39) | 0.003 |
| Male; n (%) | 4 (44) | 33 (38) | 0.8 |
| B-thal/Hb E; n (%) | 9 (69) | 67 (77) | 0.5 |
| Xerosis; n (%) | 12 (92) | 57 (66) | 0.059 |
| Hyperpigmentation; n (%) | 6 (46) | 29 (33) | 0.4 |
| Regular moisturizer use; n (%) | 6 (46) | 12 (14) | 0.012 |
| Regular warm bathing; n (%) | 5 (38) | 26 (30) | 0.5 |
| Diabetes; n (%) | 1 (8) | 5 (6) | 0.6 |
| Thyroid disorder; n (%) | 0 (0) | 8 (9) | 0.6 |

IQR=interquartile range; β-thal=β-thalassemia; Hb E=hemoglobin E

The authors found that xerosis was the most common cutaneous manifestation in thalassemia patients, which is consistent with previous reports[5-7]. Various external and internal factors can cause xerosis. External factors include environment, occupation, and skin cleansing habits, while internal factors include dermatological diseases for atopic dermatitis, internal diseases, diet, and medications. Hematologic diseases, such as myeloproliferative diseases, lymphoma, and myeloma are also associated with xerotic skin[19]. Xerosis cutis has also been reported in patients with thalassemia, which may be explained by iron overload, although the mechanism is unclear[4-10]. This is supported by reports of ichthyosis-like skin changes in patients with idiopathic hemochromatosis that improved after phlebotomy[20]. Moreover, iron excess can result in premature skin aging, as it increases the production of reactive oxygen species[21].

The authors also found that lentigines, scarring, and hyperpigmentation were common in adult thalassemia patients, consistent with the previous studies[7,8,10]. However, hyperpigmentation was more commonly found in β-thal/Hb E than non-β-thal/Hb E patients and was associated with extramedullary erythropoiesis, xerosis, and serum ferritin. This may be due to the fact that most β-thal/Hb E patients in the present study had TDT thalassemia, as evidenced by the presentation of extramedullary erythropoiesis. This condition can lead to secondary hemochromatosis, which was confirmed by high serum ferritin levels and subsequent hyperpigmentation. Previous studies had found hyperpigmentation to be common in idiopathic hemochromatosis patients[20] and associated with serum ferritin levels[7-9]. Although hyperpigmentation in hemochromatosis is the result of both hemosiderin that gives a bluish color, and melanin that results in brownish coloration, melanin is thought to play a predominant role[22,23]. Iron can upregulate various genes involved in melanogenesis, including microphthalmia-associated transcription factor (MITF), which is the master regulator of the process[24]. High plasma ACTH levels can also stimulate melanogenesis in thalassemia patients[25]. Furthermore, the authors surmise that there may be subclinical inflammation in thalassemic skin, leading to an increase in melanin production, altering melanin deposition, which in turn results in post-inflammatory hyperpigmentation[26].

Previous studies have found pruritus to be the most common presentation in patients with thalassemia[4,8,10]. This may be explained by xerosis and iron deposits in the skin. Increased nerve density has been observed in the epidermis of patients with xerosis, which could potentially contribute to the development of pruritus[27]. Studies also suggest that iron deposits in the skin may directly activate C-nerve fibers or stimulate mast cells to release histamine[28]. A previous case report described a patient with dysmetabolic hyperferritinemia that presented with generalized pruritus, which improved after treatment with phlebotomy and normalization of serum ferritin[29]. However, evidence of iron's role in pruritus is contradictory. While iron overload disorders such as hemochromatosis are associated with pruritus, iron deficiency anemia can also result

in pruritus and is actually more common[30]. In the present study, pruritus was found in only 13% of the patients, although 69% had xerosis. This might be because the present study patients had a higher average itch perception threshold than the general population. Patients with pruritus were also older than those without and were more likely to regularly use moisturizer. Elderly patients may be more likely to suffer from pruritus due to skin barrier dysfunction, immunosenescence, and neuropathy[31]. A previous animal study found that ageing skin is depleted of Merkel cells, which normally protect against touch-induced itch (alloknesis)[32].

Two patients had active leg ulcers and another 14 had a history of leg ulcers, which may have been due to skin iron overload. Dermal deposition of hemosiderin causes activation of iron-dependent M1 macrophages, leading to the production of reactive oxygen species and inflammatory cytokines, including TNF-α and IL-6, as well as the activation of matrix metalloproteinase and fibroblast senescence. Together, these factors contribute to tissue breakdown and poor wound healing[33].

Although previous studies have reported clinical and laboratory findings in thalassemia patients, none have evaluated dermatology-specific health-related QoL[5-10]. The median DLQI score of the thalassemia patients in the present study was 0 (IQR 0, 2), while a previous study reported a mean DLQI score of 6.3 in Thai systemic sclerosis patients[34]. This may be due to pain, pruritus, skin sclerosis, and hand contracture caused by systemic sclerosis. A previous study used the World Health Organization Quality of Life Brief Version (WHOQOL-BREF) to assess QoL of adult thalassemia patients in Malaysia and found that the personal relationship domain in the DLQI (mean summation of questions 8 and 9 of 0.01 with a maximum of 3, higher score indicates larger effect) was comparable to the social relationship domain of the WHOQOL-BREF (mean 64.0, a score closer to 100 indicates a better quality)[35]. This implies that cutaneous changes had a little impact on thalassemia patients' QoL.

One limitation of the present study was its cross-sectional design, in which some short-lived skin lesions, such as infections or transient inflammatory dermatosis, may have been missed, resulting in a low proportion of these dermatoses in the present study population. Second, the present study was performed in a single center, the results might differ from those in other regions. Third, despite using the operational definitions for cutaneous manifestations, assessment was mostly subjective, which poses a risk of bias. Results may be more reliable if based on objective assessment of biophysical parameters such as transepidermal water loss, melanin pigmentation, or elasticity. Furthermore, some details, including duration of sun exposure per day, frequency of sunscreen use, and over-the-counter medications that might affect hyperpigmentation, were not collected or utilized due to the invalidity of information.

The present study is the first study of cutaneous manifestations in adults to include a high proportion of β-thal/Hb E patients. Xerosis was the most common cutaneous finding, and hyperpigmentation was more commonly observed in patients with β-thal/Hb E. However, cutaneous changes had a low impact on patients' QoL.

## What is already known on this topic?

There are various cutaneous manifestations in thalassemia patients including xerosis, pruritus, idiopathic guttate hypomelanosis, and urticaria. Most studies have focused on children with β-thalassemia major.

## What does this study add?

Xerosis was the most common cutaneous finding in adult thalassemia patients. Hyperpigmentation was more common in patients with β-thal/Hb E than those without.


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## Authors' contributions

NJ, NT, and SC conceived and designed the study and reviewed the manuscript. NJ and SC analyzed the data and interpreted the results. NJ and SC drafted the manuscript. NJ and SC analyzed and interpreted the data and edited, revised, and approved the final version of the manuscript. NJ, CC, RW, NT, and SC were responsible for confirming the authenticity of the raw data. All authors read and approved the final manuscript.


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## Conflicts of interest

The authors declare no conflict of interest.

## References


1. Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood 2010;115:4331-6.
2. Sankaran VG, Nathan DG. Thalassemia: an overview of 50 years of clinical research. Hematol Oncol Clin North Am 2010;24:1005-20.
3. Chuncharunee S, Teawtrakul N, Siritanaratkul N, Chueamuangphan N. Review of disease-related complications and management in adult patients with thalassemia: A multi-center study in Thailand. PLoS One 2019;14:e0214148.
4. Gaber M, Galal M. Cutaneous manifestation of β-thalassemic patients. Menoufia Med J 2020;33:267-71.
5. Roy K, Das SK, Dutta A, Mandal RK. Dermatological manifestations in beta thalassemia major patients between 2 to 12 years and their relation with serum ferritine level. New Indian J Pediatr 2018;7:149-57.
6. El-Dash H, Adel S. Cutaneous manifestations in Egyptian children with beta-thalassemia major: Relationship with serum ferritin, thyroid profile, and treatment modalities. Pediatr Dermatol 2018;35:639-43.
7. Pektas SD, Alatas ET, Pektaş G, Karakuş V, Azık FM, Doğan G. Analysis of skin, hair and nail diseases in the adults with beta thalassemia major. Gazi Med J 2018;29:128-33.
8. Fahmey SS, Taha G, El-Refaey A, Adly S. Skin Disorders in Egyptian Children with β-Thalassemia Major. J Trop Pediatr 2018;64:104-9.
9. Kerim SI, Hasan KM. Cutaneous manifestation among patients with β- thalassemia major. Iraq J Hematol 2014;3:98-107.
10. Dogramaci AC, Savas N, Ozer B, Duran N. Skin diseases in patients with beta-thalassemia major. Int J Dermatol 2009;48:1057-61.
11. Weatherall DJ. The definition and epidemiology of non-transfusion-dependent thalassemia. Blood Rev 2012;26 Suppl 1:S3-6.
12. Kulthanan K, Jiamton S, Wanitphakdeedecha R, Chantharujikaphong S. The validity and reliability of the Dermatologic Life Quality Index (DLQI) in Thais. Thai J Dermatol 2004;20:113-23.
13. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.
14. R Foundation for Statistical Computing. R: A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2021 [cited 2022 Aug 14]. Available from: https://www.R-project.org/.
15. Sirlin CB, Reeder SB. Magnetic resonance imaging quantification of liver iron. Magn Reson Imaging Clin N Am 2010;18:359-81, ix.
16. Walker M, Wood J. Cardiac complications in thalassaemia major. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, editors. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 3rd ed. Nicosia, CY: Thalassaemia International Federation; 2014 [cited 2022 Aug 14]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK269371/.
17. Maron BA, Brittain EL, Choudhary G, Gladwin MT. Redefining pulmonary hypertension. Lancet Respir Med 2018;6:168-70.
18. Triadyaksa P, Oudkerk M, Sijens PE. Cardiac T(2) * mapping: Techniques and clinical applications. J Magn Reson Imaging 2020;52:1340-51.
19. Augustin M, Wilsmann-Theis D, Körber A, Kerscher M, Itschert G, Dippel M, et al. Diagnosis and treatment of xerosis cutis - a position paper. J Dtsch Dermatol Ges 2019;17 Suppl 7:3-33.
20. Chevrant-Breton J, Simon M, Bourel M, Ferrand B. Cutaneous manifestations of idiopathic hemochromatosis. Study of 100 cases. Arch Dermatol 1977;113:161-5.
21. Polla AS, Polla LL, Polla BS. Iron as the malignant spirit in successful ageing. Ageing Res Rev 2003;2:25-37.
22. Cawley EP, Hsu YT, Wood BT, Weary PE. Hemochromatosis and the skin. Arch Dermatol 1969;100:1-6.
23. Maize JC Sr, Ralston JS. Metabolic diseases of the skin. In: Elder DE, editor. Lever's Histopathology of the skin. 11th ed. Philadelphia, PH: Wolters Kluwer; 2015. p. 502-44.
24. Wolkow N, Li Y, Maminishkis A, Song Y, Alekseev O, Iacovelli J, et al. Iron upregulates melanogenesis in cultured retinal pigment epithelial cells. Exp Eye Res 2014;128:92-101.
25. McIntosh N. Endocrinopathy in thalassaemia major. Arch Dis Child 1976;51:195-201.
26. Lawrence E, Al Aboud KM. Postinflammatory hyperpigmentation. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2022 [cited 2023 Feb 7]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559150/.
27. Moniaga CS, Tominaga M, Takamori K. Mechanisms and management of itch in dry skin. Acta Derm Venereol 2020;100:adv00024.
28. Nestler JE. Hemochromatosis and pruritus. Ann Intern Med 1983;98:1026.
29. Brigant F, Hautefeuille V, Dadban A, Lok C, Nguyen-Khac E, Chaby G. Generalized pruritus in dysmetabolic hyperferritinemia treated by phlebotomy. Dermatol Online J 2015;21:13030/qt4qg8m234.
30. Roh YS, Choi J, Sutaria N, Kwatra SG. Itch: Epidemiology, clinical presentation, and diagnostic

workup. J Am Acad Dermatol 2022;86:1-14.
31. Chung BY, Um JY, Kim JC, Kang SY, Park CW, Kim HO. Pathophysiology and treatment of pruritus in elderly. Int J Mol Sci 2020;22:174.
32. Feng J, Luo J, Yang P, Du J, Kim BS, Hu H. Piezo2 channel-Merkel cell signaling modulates the conversion of touch to itch. Science 2018;360:530-3.
33. Wright JA, Richards T, Srai SK. The role of iron in the skin and cutaneous wound healing. Front Pharmacol 2014;5:156.
34. Chularojanamontri L, Sethabutra P, Kulthanan K, Manapajon A. Dermatology life quality index in Thai patients with systemic sclerosis: a cross-sectional study. Indian J Dermatol Venereol Leprol 2011;77:683-7.
35. Foong WC, Chean KY, Rahim FF, Goh AS, Yeoh SL, Yeoh AAC. Quality of life and challenges experienced by the surviving adults with transfusion dependent thalassaemia in Malaysia: a cross sectional study. Health Qual Life Outcomes 2022;20:2.