# The validity of pallor as a clinical sign of anemia in cases with beta-thalassemia

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**SUMMARY: Yalçın SS, Ünal S, Gümrük F, Yurdakök K. The validity of pallor as a clinical sign of anemia in cases with beta-thalassemia. Turk J Pediatr 2007; 49: 408-412.**

**Pallor is deemed useful in the evaluation of patients suspected of anemia, although its perceived presence or absence may be misleading in cases with increased pigmentation with iron, melanin, or bilirubin. The purpose of this study was to determine the validity of pallor in the detection of anemia in children with beta-thalassemia as an iron overload model. Patients with beta-thalassemia A aged 2 to 32 years who were admitted to the Hematology Unit, Department of Pediatrics, İhsan Doğramacı Children's Hospital, Ankara, Turkey were assessed for the presence of pallor in three anatomic sites (palm, conjunctiva, buccal mucosa) by a trained pediatrician. Overall, 105 observations were done. The mean age of the patients was 14.7±6.5 years. The mean hemoglobin (Hb) value was 10.0±1.2 g/dl (range: 5.4–12.6 g/dl). The sensitivities of palmar, buccal and conjunctival pallor for identifying thalassemic children with anemia were 93.2, 80.7 and 90.9%, respectively. Cases with Hb values less than 11 g/dl could be easily detected by conjunctival pallor, independent of serum ferritin levels. However, there were significant associations between the presence of palmar or buccal pallor and the presence of anemia in children with serum ferritin levels lower than 2500 μg/L. Palmar pallor alone had the highest sensitivity and lowest specificity to detect anemia in cases with beta-thalassemia. Conjunctival pallor was more useful than buccal and palmar pallor in cases with high ferritin levels. Further studies are necessary to detect the validity of pallor in different underlying diseases with anemia.**

***Key words: beta-thalassemia, pallor, anemia.***

The diagnosis and management of anemia, which affects a significant proportion of young children in developing countries, largely depends on the clinical assessment of pallor. Recommendations based on hemoglobin (Hb) values are useful for managing children when Hb can be measured; however, laboratory measurements are often not available in the usual clinical settings in developing countries. Pallor is deemed useful in the evaluation of patients suspected of anemia, although its perceived presence or absence may be misleading for a variety of reasons including increased pigmentation with iron, melanin, or bilirubin[1-5]. There is a limited number of published studies about the effect of hyperpigmentation on the validity of pallor[2,6,7] and no published study about iron overload.

Beta-thalassemia is a chronic, genetically determined hematological disorder characterized by ineffective erythropoiesis, peripheral hemolysis and severe anemia. In patients with beta-thalassemia, irregular transfusions, incompatibility of chelation therapy, increased absorption of iron from the gastrointestinal tract, and chronic hypoxic situation lead to increased iron overload and damage to visceral organs. Additionally, the increased iron overload causes hyperpigmentation by accumulation of iron in the skin[8]. Therefore, cases with beta-thalassemia, having iron overload, can be used to detect the effect of increased pigmentation on the validity of pallor.

The evaluation of pallor of the conjunctivae, face, mucous membranes and palms is recommended for the detection of anemia[4]. Whether palmar

or conjunctival pallor performs better depends in part on other conditions. In Bangladesh, for example, greater palmar pigmentation was associated with very low sensitivity of palmar pallor as a single sign[6], whereas high rates of conjunctivitis in Ethiopia obscured conjunctival pallor and led to an adaptation of the guidelines to require either conjunctival or palmar pallor[9]. However, the World Health Organization (WHO) recommends the evaluation of palmar pallor as an indication of anemia in their Integrated Management of Childhood Illnesses (IMCI)[10]. Therefore, the present study evaluates the validity of palmar, conjunctival and buccal pallor to identify beta-thalassemic children with anemia as an iron overload model.

## Material and Methods

Patients with beta-thalassemia aged 2 to 32 years who were admitted to the Hematology Unit, Department of Pediatrics, İhsan Doğramacı Children's Hospital, Ankara, Turkey were assessed for the presence of pallor in three anatomic sites (palm, conjunctiva, buccal mucosa) by a trained pediatrician. Cases with any acute or chronic illness besides beta-thalassemia were excluded from the study. All observations were made without any information about the children's hematological status. Anemia status of the subjects was evaluated by physical examination included in the IMCI protocol[9]. Conjunctival and oral mucosal pallor were rated as absent or present. Conjunctival pallor was evaluated by everting the lower eyelid and examining the palpebral conjunctiva, and the buccal mucosa was examined for pallor by natural light. Palmar pallor was rated as none, some or severe. Palmar pallor was assessed over thenar eminence without extending the fingers.

Venous blood samples (4 ml) were obtained to assess complete blood counts [hemoglobin (Hb), mean corpuscular volume (MCV), red blood cell count (RBC), red cell distribution width (RDW)] and serum ferritin, and complete blood counts were determined by a Coulter Counter-S model (Coulter®; STKS, Coulter Corp., Hialeah, FL, USA). Serum ferritin was measured by a commercial kit (Tina quant® a ferritin(e), Lot no: 62159101-62376101, Preciset ferritin(e), Lot no: 61043462, Roche, USA) with the Modular Analytic System (ROCHE Diagnostics/HITACHI (Modular DP), Japan).

Data were analyzed using SPSS for Windows (SPSS Inc., Chicago, IL, USA). Anemia was defined as Hb level lower than 11 g/dl. The performance (sensitivity, specificity, and positive predictive value) of the pallor in identifying cases with anemia was determined by comparison with Hb levels below a specified cutoff level. Significance of differences in proportions was determined using Pearson's chi-square test, Mantel-Haenszel chi-square test and Fisher's exact test, where appropriate.

## Results

Overall, 105 observations were done during the three months of the study period. The mean age was 14.7±6.5 years (median: 15.4 years) and 50.5% were male. The mean Hb value was 10.0±1.2 g/dl (range: 5.4-12.6 g/dl); 88 (83.8%) were <11.0 g/dl, and 53 (50.5%) <10.0 g/dl (Table I). The median value of ferritin was 2480 µg/L (range: 1044-8000 µg/L).

**Table I.** Age and Complete Blood Counts of Cases

| | Mean ± SD | Range |
|---|---|---|
| Age (years) | 14.7 ± 6.5 | 2.2 - 31.9 |
| Hb (g/dl) | 10.0 ± 1.2 | 5.4 - 12.6 |
| Htc (%) | 29.1 ± 3.8 | 15.6 - 39.7 |
| RBC (X $10^9$/$mm^3$) | 3.50 ± 0.53 | 1.97 - 5.40 |
| Ferritin (µg/L) | 2873 ± 1349 | 1044 - 8000 |

Hb: Hemoglobin. Htc: Hematocrit. RBC: Red blood cells.

The sensitivities of palmar, buccal and conjunctival pallor for identifying beta-thalassemic children with anemia were 93.2, 80.7 and 90.9%, respectively (Table II). Palmar pallor had the highest sensitivity in detecting anemia compared to the other anatomic sites and had the lowest specificity. The presence of pallor in any two of the three anatomic sites had the highest specificity (70.6%). Decreasing the cut-off point for Hb from 11 to 10 g/dl only affected the sensitivity of pallor of buccal mucosa.

The association between Hb (≥11 g/dl versus <11 g/dl) and some or severe palmar pallor was studied, controlling for gender (Table III). Regardless of gender, Hb was inversely associated with the presence of pallor (odds ratio-OR: 0.174, confidence interval-CI: 0.046-0.660; p=0.017), and this association was statistically significant in female cases (p=0.026). However, after controlling for gender, Hb was inversely

**Table II.** Sensitivity, Specificity, and Positive Predictive Values of Clinical Signs to Detect Children with Anemia among Beta-Thalassemia Cases

| Clinical sign (sites checked for pallor) | n | % | Hb <11 g/dl | | | Hb <10 g/dl | | |
|---|---|---|---|---|---|---|---|---|
| | | | Sensitivity | Specificity | PPV | Sensitivity | Specificity | PPV |
| Palmar pallor | 94 | 89.5 | 93.2 | 29.4 | 87.2 | 94.3 | 15.4 | 53.2 |
| Conjunctival pallor | 88 | 83.8 | 90.9 | 52.9 | 90.9 | 88.7 | 40.4 | 60.3 |
| Buccal mucosa pallor | 78 | 74.3 | 80.7 | 58.8 | 91.0 | 94.3 | 26.9 | 56.8 |
| Palmar and conjunctival pallor | 50 | 47.6 | 51.1 | 70.6 | 90.0 | 56.6 | 61.5 | 60.0 |
| Palmar and buccal pallor | 52 | 49.5 | 53.4 | 70.6 | 90.4 | 58.5 | 59.6 | 59.6 |
| Buccal and conjunctival pallor | 74 | 70.5 | 78.4 | 70.6 | 93.2 | 86.8 | 46.2 | 62.2 |
| Palmar, buccal and conjunctival pallor | 50 | 47.6 | 51.1 | 70.6 | 90.0 | 56.6 | 61.5 | 60.0 |

Hb: Hemoglobin. PPV: Positive predictive values.

**Table III.** Associations Between Hb Value (<11 Versus ≥11 g/dl) and Pallor Controlling for Gender and Age (<10 versus ≥10 years)

| | Conjunctival pallor | | | | Buccal mucosal pallor | | | | Some-severe palmar pallor | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n/T | % | OR (95%CI) | p | n/T | % | OR (95%CI) | p | n/T | % | OR (95%CI) | p |
| Male | | | 0.113 (0.020-0.632) | 0.018 | | | 0.194 (0.044-0.855) | 0.036 | | | 0.300 (0.043-2.095) | 0.235 |
| Hb<11 (ref.) | 40/43 | 93.0 | | | 36/43 | 83.7 | | | 40/43 | 93.0 | | |
| Hb≥11 | 6/10 | 60.0 | | | 5/10 | 50.0 | | | 8/10 | 80.0 | | |
| Female | | | 0.050 (0.008-0.329) | 0.002 | | | 0.114 (0.019-0.680) | 0.016 | | | 0.095 (0.014-0.637) | 0.026 |
| Hb<11 (ref.) | 40/45 | 88.9 | | | 35/45 | 77.8 | | | 42/45 | 93.3 | | |
| Hb≥11 | 2/7 | 28.6 | | | 2/7 | 28.6 | | | 4/7 | 57.1 | | |
| Mantel-Haenszel | | | 0.077 (0.022-0.273) | <0.001 | | | 0.155 (0.050-0.479) | 0.002 | | | 0.174 (0.046-0.660) | 0.017 |
| Age<10 | | | | 0.001 | | | 0.059 (0.005-0.680) | 0.020 | | | 0.070 (0.007-0.705) | 0.034 |
| Hb<11 (ref.) | 18/21 | 85.7 | | | 17/21 | 81.0 | | | 19/21 | 90.5 | | |
| Hb≥11 | 0/5 | 0.0 | | | 1/5 | 20.0 | | | 2/5 | 40.0 | | |
| Age≥10 years | | | 0.161 (0.036-0.728) | 0.026 | | | 0.241 (0.067-0.869) | 0.033 | | | 0.317 (0.051-1.967) | 0.224 |
| Hb<11 (ref.) | 62/67 | 92.5 | | | 54/67 | 80.6 | | | 63/67 | 94.0 | | |
| Hb≥11 | 8/12 | 66.7 | | | 6/12 | 50.0 | | | 10/12 | 83.3 | | |
| Mantel-Haenszel | | | 0.077 (0.021-0.277) | <0.001 | | | 0.170 (0.057-0.510) | 0.002 | | | 0.174 (0.045-0.672) | 0.011 |

OR: Odds ratio. CI: Confidence interval. Hb: Hemoglobin.

associated with conjunctival and mucosal pallor (Mantel-Haenszel chi-square test, p<0.001, p=0.002, respectively), and this association was statistically significant in both male and female cases. The association between Hb values (≥11 g/dl versus <11 g/dl) and pallor was studied, controlling for age (≥10 years of age versus <10). After controlling for age, Hb was shown to be inversely associated with pallor (Mantel-Haenszel chi-square test, p<0.001 for conjunctival pallor, p<0.002 for mucosal pallor, p=0.011 for palmar pallor). However, there was no correlation between palmar pallor and Hb value in older cases (Table III). Similarly, the association between Hb value (≥11 g/dl versus <11 g/dl) and pallor was also analyzed, controlling for ferritin levels (Table IV). Mantel-Haenszel chi-square test was significant (p= 0.037 for some-severe pallor, p=0.002 for buccal mucosal pallor), and this association was only statistically significant in cases with ferritin lower than 2500 µg/L. Regardless of the ferritin levels, there were more cases with anemia in cases with conjunctival pallor (p=0.001 for cases with low ferritin levels, p=0.040 for cases with high ferritin levels, Mantel-Haenszel chi-square test, p<0.001).

**Table IV.** Associations Between Hb Value (<11 versus ≥11 g/dl) and Pallor Controlling for Ferritin (<2500 versus ≥2500 µg/L)

| | Conjunctival pallor | | | | Buccal mucosal pallor | | | | Some-severe palmar pallor | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n/T | % | OR (95%CI) | p | n/T | % | OR (95%CI) | p | n/T | % | OR (95%CI) | p |
| Ferritin<2500 | | | 0.064 (0.012-0.340) | 0.001 | | | 0.156 (0.037-0.653) | 0.011 | | | 0.092 (0.017-0.490) | 0.006 |
| Hb<11 (ref.) | 39/42 | 93 | | | 33/42 | 79 | | | 39/42 | 93 | | |
| Hb≥11 | 5/11 | 46 | | | 4/11 | 36 | | | 6/11 | 55 | | |
| Ferritin≥2500 | | | 0.122 (0.019-0.776) | 0.040 | | | 0.211 (0.036-1.239) | 0.101 | | | | 1.000 |
| Hb<11 (ref.) | 41/46 | 89 | | | 38/46 | 83 | | | 43/46 | 94 | | |
| Hb≥11 | 3/6 | 50 | | | 3/6 | 50 | | | 6/6 | 100 | | |
| Mantel-Haenszel | | | 0.084 (0.025-0.287) | <0.001 | | | 0.174 (0.057-0.529) | 0.002 | | | 0.186 (0.048-0.719) | 0.037 |

OR: Odds ratio. CI: Confidence interval. Hb: Hemoglobin.

## Discussion

In this study, pallor was found to be sensitive in beta-thalassemic cases when used by a pediatrician. However, palmar pallor was affected by gender, age and ferritin levels. Interestingly, conjunctival pallor did not change with these factors. Rees et al.[11] reported that hyperpigmentation becomes evident with age in adolescent patients with beta-thalassemia who are incompatible with chelation therapy iron overload. However, in our study, there was no correlation between age and ferritin levels. Therefore, the change in validity of pallor with age could not be explained by ferritin levels in our study. This might be explained by changes in skin characteristics with age and sex. Previously, Seidenari et al.[12] also reported that there was a great regional variation in the behavior of ultrasound reflection of elderly skin (older than 60) with respect to the skin of young subjects (27-30 years of age) in a study which was employed to assess skin thickness. Some changes might occur in skin characteristics from childhood to adolescence.

Pallor in cases with high ferritin levels could be evaluated by the examination of conjunctiva mucosa. Similarly, in previous studies, palmar pallor was found to be more useful than buccal and conjunctival pallor except in dark skinned and black subjects[2,6,7]. In Bangladesh, palmar pallor had lower sensitivity than conjunctival pallor probably because of dark palmar pigment[6]. In Pakistan, conjunctival pallor had the highest sensitivity of all sites for detecting anemia[13]. Studies in Africa[14,15] and of whites in the United States[2] have shown that the nail beds and palm are the best sites for assessing pallor.

Previous studies have revealed controversial results concerning the validity of combining pallor at more than one anatomic site[6,9]. In this study, overall, the checking of pallor at one site alone was better than the combination of two sites, which reduced sensitivity and increased specificity.

In the present study, the sensitivity levels for two different Hb values (11 and 10 g/dl) were similar. However, compared to mild anemia, the sensitivity of clinical pallor was reported to be increased in children with moderate-severe anemia[2,7,16]. In our study, the cases with moderate-severe anemia were limited.

The training course on IMCI focused upon the assessment, classification, and treatment of sick children aged 2 months to 5 years[10]; however, in this study, for the first time, the validity of pallor was studied in cases with beta-thalassemia aged between 2-32 years. The validity of pallor in beta-thalassemia was very similar to that seen in healthy children in detecting anemia. The findings of the study suggest that conjunctival pallor has adequate sensitivity and specificity to detect anemia regardless of age, gender and serum ferritin levels in cases with beta-thalassemia. The validity of palmar pallor should be evaluated along with the age, sex and serum ferritin levels of beta-thalassemic cases. The validity of buccal mucosal pallor might be affected by serum ferritin levels, and therefore, cases with iron overload might be evaluated through assessment of conjunctival pallor. In conclusion, the present study demonstrates that clinical criteria in cases with beta-thalassemia can be used to identify children with anemia, thus enabling implementation of treatment algorithms even when urgent Hb measurements are not available.

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