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A Multimethod Analysis of Thyroid Hormone Profiles and Growth Indicators in Pediatric β-Thalassemia Major: A Study in Indonesia

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ABSTRACT

Children with thalassemia are at increased risk of growth impairment and endocrine dysfunction, including thyroid abnormalities. However, the relationship between thyroid function and stunting remains unclear. This cross-sectional study included 51 children with confirmed thalassemia. Growth status was assessed using height-for-age Z-score (HAZ) and percentage height deficit relative to mid-parental target height (Mid-TPG), while thyroid function was evaluated by measuring serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4). Data were analyzed using Pearson or Spearman correlation, multivariable linear regression, locally estimated scatterplot smoothing (LOESS), generalized additive models (GAM), and k-means clustering. No significant associations were found between thyroid hormone levels and either HAZ or height deficit in multivariable analyses (all $p > 0.05$). FT4 showed a weak positive correlation with HAZ ($\rho = 0.265$), although it was not statistically significant ($p = 0.06$). LOESS and GAM demonstrated limited explanatory power. K-means clustering identified three distinct growth phenotypes with significant differences in HAZ and height deficit ($p < 0.001$), whereas TSH and FT4 levels did not differ across clusters. These findings suggest that thyroid hormone levels are not significantly associated with stunting severity in children with β-thalassemia major, highlighting the multifactorial nature of growth impairment and the need for further investigation to support targeted intervention strategies.

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
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INTRODUCTION

Thalassemia-β mayor is one of the most prevalent inherited hemoglobinopathies worldwide, particularly in Southeast Asia, the Middle East, and the Mediterranean regions (Kattamis et al., 2020). Advances in transfusion therapy and iron chelation have significantly improved the life expectancy of children with thalassemia; however, complications such as growth failure and endocrine dysfunction remain substantial concerns (Carsote et al., 2022; Malik et al., 2023). Stunting is frequently observed in this population and is multifactorial in origin, often attributed to chronic anemia, iron overload, nutritional deficiencies, and disturbances in hormonal regulation (Nisa et al., 2023; Soliman et al., 2023).

Among endocrine abnormalities, thyroid dysfunction is commonly reported in transfusion-dependent thalassemia patients, particularly hypothyroidism, which may manifest subclinically or overtly due to iron deposition in the thyroid gland (Carsote et al., 2022; Mahmoud et al., 2021). Thyroid hormones play a crucial role in childhood growth and skeletal development; thus, impaired thyroid function could exacerbate the risk of stunting in this vulnerable group (Hussein, 2022). However, the relationship between thyroid function—particularly serum thyrotropin (TSH) and free thyroxine (FT4) levels—and anthropometric indicators like height-for-age Z-score (HAZ) and height deficit in children with thalassemia-β mayor remains incompletely understood.

Previous studies have highlighted the prevalence of growth impairment and thyroid dysfunction individually, but few have investigated their interrelationship using integrative statistical approaches such as correlation, regression, and clustering analyses. Moreover, there is limited information on whether variations in thyroid profile are associated with distinct growth patterns among children with thalassemia-β mayor in Indonesia, where disease burden is high, and screening programs remain variable (Wahidiyat et al., 2022). This study aims to explore the association between thyroid function and growth status in children with thalassemia-β mayor by analyzing the relationship of TSH and FT4 levels with HAZ and height deficit. Using both conventional and machine-learning-based approaches, including unsupervised clustering and non-linear modeling, we seek to identify potential subgroups and patterns that may inform targeted interventions for growth monitoring and endocrine screening in this population.

RESEARCH METHOD

This cross-sectional observational study included 51 children diagnosed with thalassemia-β mayor, recruited from Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. Inclusion criteria comprised children aged 6–18 years with a confirmed diagnosis of transfusion-dependent thalassemia, a stable clinical condition, and regular follow-up. Children with known endocrine disorders unrelated to thalassemia, those undergoing hormonal therapy (e.g., growth hormone or thyroid replacement), or receiving growth-affecting supplements were excluded.

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
JURNAL RAGAM PENGABDIAN - PENELITIAN

Additionally, children with other chronic conditions affecting growth, such as renal or cardiac disease, were not included.

The study protocol was reviewed and approved by the Health Research Ethics Committee of Dr. Zainoel Abidin General Hospital (RSUDZA), Banda Aceh (Approval No: 001/ETIK-RSUDZA/2023, approved on January 11, 2023). The approval was granted in accordance with the seven standards of WHO 2011 and CIOMS 2016 guidelines, and was valid for the period from January 2, 2023 to January 2, 2024. Written informed consent was obtained from parents or legal guardians of all participants, with assent provided by children as appropriate. The research was conducted in compliance with the principles of the Declaration of Helsinki, ensuring protection of human rights, welfare, and confidentiality of participant data.

Anthropometric measurements, including height (in centimeters), were recorded using a calibrated stadiometer. Age- and sex-specific height-for-age Z-scores (HAZ) were calculated based on WHO reference standards using WHO AnthroPlus. Height deficit (%) was computed as the percentage difference between the actual height and mid-parental target height (Mid TPG). Mid TPG was estimated as follows:

For boys: (Father's height + Mother's height + 13 cm)/2
For girls: (Father's height + Mother's height - 13 cm)/2

Venous blood samples were obtained after an overnight fast to evaluate thyroid function. Serum TSH and FT4 concentrations were determined using the enzyme-linked immunofluorescent assay (ELFA) method, with reference ranges of 0.25–5 μIU/mL for TSH and 9–20 pmol/L for FT4. All measurements were performed in the central laboratory of Dr. Zainoel Abidin General Hospital, Banda Aceh, following the manufacturer's instructions.

Data were analyzed using Rstudio version 2025.05.1. Descriptive statistics were presented as means ± standard deviation (SD) for continuous variables. Differences across clusters were assessed using one-way ANOVA or Kruskal-Wallis test depending on normality. K-means clustering was performed on standardized values of HAZ and height deficit to identify subgroups with distinct growth profiles. The optimal number of clusters was determined using the elbow method.

Pearson and Spearman correlation coefficients were calculated to examine associations between thyroid function and growth parameters. Linear regression models were used to identify predictors of HAZ and height deficit, adjusting for age and sex. In addition, generalized additive models (GAM) and locally estimated scatterplot smoothing (LOESS) were applied to explore nonlinear relationships between variables. A p-value <0.05 was considered statistically significant.All figures were created using ggplot2 and mgcv packages in Rstudio.

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
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RESULTS AND DISCUSSION

Characteristics of the research subjects

A total of 51 children with β-thalassemia major were included, where 54.9% of them were boys. The mean age was 12.98 ± 2.85 years, and the average height was 139.58 ± 11.55 cm. The mean HAZ was -1.89 ± 1.16, indicating mild to moderate stunting. The mean height deficit was 15.14 ± 7.89%, and the mid-parental target height (Mid TPG) was 164.76 ± 6.81 cm. Thyroid profiles showed a mean TSH level of 2.82 ± 1.86 ng/mL and a mean FT4 level of 16.18 ± 2.92 ng/mL. Respondent characteristics (n = 51).

Table 1. Characteristics of the research subjects

Variable	Mean ± SD
Total, n	51
Boys, n (%)	28 (54.9)
Age (years)	12.98±2.85
Height (cm)	139.58±11.55
Height-for-age Z-score	-1.89±1.16
mid-parental target height (cm)	164.76±6.81
Height deficit (%)	15.14±7.89
TSH (ng/mL)	2.82±1.86
FT4 (ng/mL)	16.18±2.92

Linear Regression

Results from multivariable linear regression analyses are presented in Table 2. When predicting height-for-age Z-score (HAZ), the overall model was statistically significant ($F(4, 46) = 3.21$, $p = 0.021$), explaining 15% of the variance (adjusted $R^2 = 0.15$). However, neither TSH ($\beta = -0.077$, $p = 0.349$) nor FT4 ($\beta = -0.0076$, $p = 0.891$) were significant predictors of HAZ. Age was the only significant variable, showing a negative association with HAZ ($\beta = -0.194$, $p = 0.002$). Sex had no significant effect. In contrast, the regression model predicting height deficit was highly significant $F(4, 46) = 28.99$, $p < 0.001$), with a strong model fit (adjusted $R^2 = 0.691$). Older age was associated with a lower height deficit ($\beta = -1.812$, $p < 0.001$), while male sex predicted greater height deficit ($\beta = 5.687$, $p < 0.001$). TSH showed a positive but statistically non-significant association with increased height deficit ($\beta = 0.612$, $p = 0.076$), while FT4 remained non-significant ($\beta = 0.173$, $p = 0.447$).

Table 2. Results of the linear regressions

Predictor	Estimate	Std. Error	*p*-value
Predicting HAZ			
(Intercept)	1.08	1.45	0.458
TSH	-0.077	0.082	0.349
FT4	-0.0076	0.055	0.891

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
JURNAL RAGAM PENGABDIAN - PENELITIAN

Age (years)	-0.194	0.057	0.002
Sex	-0.217	0.315	0.494
Adj-R^2	0.15		
F (4, 46)	3.21		
p-value	0.021		
Predicting height deficit			
(Intercept)	31.02	5.95	<0.001
TSH	0.612	0.336	0.076
FT4	0.173	0.226	0.447
Age (years)	-1.812	0.236	<0.001
Sex	5.687	1.295	<0.001
Adj-R^2	0.691		
F (4, 46)	28.99		
p-value	<0.001		

FT4: Free thyroxine; HAZ: height-for-age Z-score; TSH, thyroid-stimulating hormone

Pearson and Spearman Correlations

Bivariate correlation results are presented in Table 3. Using Pearson's correlation, weak and non-significant relationships were observed between TSH and HAZ (r = -0.088, p = 0.541), FT4 and HAZ (r = 0.133, p = 0.354), TSH and height deficit (r = 0.152, p = 0.288), and FT4 and height deficit (r = 0.200, p = 0.159). Similarly, Spearman's rank correlation coefficients indicated slightly stronger but still non-significant monotonic associations. FT4 showed a positive but non-significant correlation with HAZ (ρ = 0.265, p = 0.060), and TSH with height deficit (ρ = 0.263, p = 0.063), although neither reached the threshold for statistical significance.

Table 3. Results of Pearson and Spearman correlations

Variable pair	**Estimates**	
Pearson	r	p-value
TSH vs HAZ	-0.088	0.541
FT4 vs HAZ	0.133	0.354
TSH vs Height Deficit	0.152	0.288
FT4 vs Height Deficit	0.2	0.159
Spearman	ρ	p-value
TSH vs HAZ	-0.106	0.461
FT4 vs HAZ	0.265	0.06
TSH vs Height Deficit	0.263	0.063
FT4 vs Height Deficit	0.205	0.15

FT4: Free thyroxine; HAZ: height-for-age Z-score; TSH, thyroid-stimulating hormone

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
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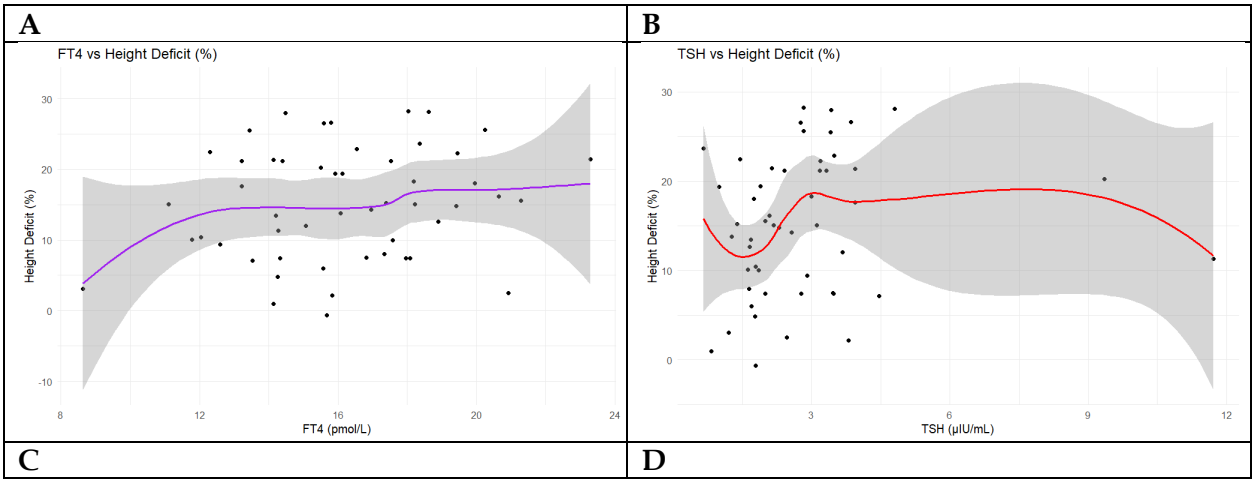
LOESS Regression

LOESS smoothing curves are presented in Figure 1. The regression revealed subtle nonlinear associations between FT4 and TSH with both height deficit and HAZ. Among the four variable pairs, TSH showed the most apparent curvature when plotted against height deficit and HAZ, suggesting potential thresholds or inflection points. However, pseudo-R^2 values were modest across all models, with the highest observed for TSH vs height deficit (pseudo-R^2 = 0.15) (Table 4). FT4 showed relatively flat trends with both growth metrics (pseudo-R^2 = 0.076), while TSH vs HAZ also yielded a weak association (pseudo-R^2 = 0.055). Residual standard errors were comparable across models, ranging from 1.17 to 8.03 (Table 4).

Table 4. LOESS results for various variable pairs

Variable pair	Residual SE	Effective df	Pseudo-R^2
TSH vs HAZ	1.194	5.58	0.055
FT4 vs HAZ	1.176	5.33	0.076
TSH vs Height Deficit	7.725	5.58	0.15
FT4 vs Height Deficit	8.025	5.33	0.076

FT4: Free thyroxine; HAZ: height-for-age Z-score; SE, standard error; TSH, thyroid-stimulating hormone



eISSN 3063-802X & pISSN 3063-8011
JURAGAN
JURNAL RAGAM PENGABDIAN - PENELITIAN

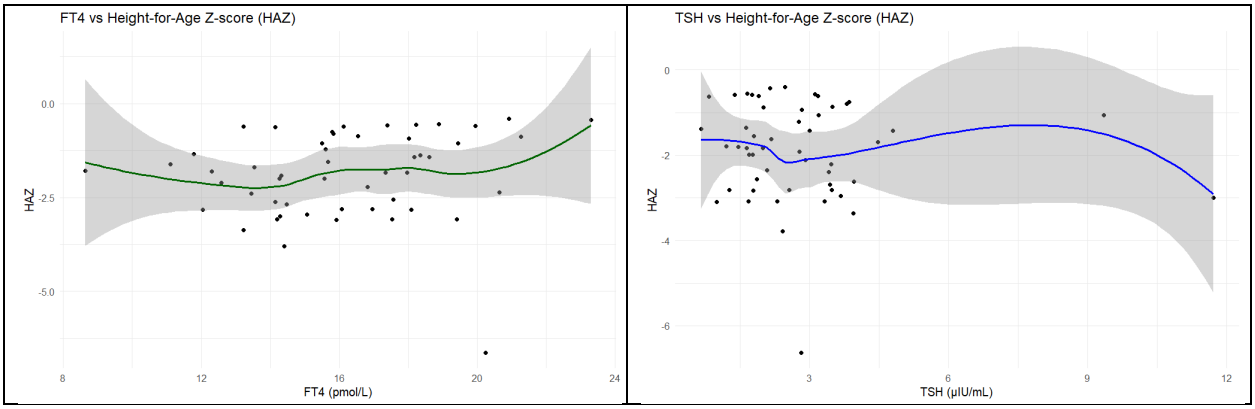


Figure 1. LOESS graphs depicting relationships between FT4 and height deficit (a), TSH and height deficit (b), FT4 and HAZ (c), as well as TSH and HAZ (d)

GAM Models

Graphs for GAM models fitted with HAZ and height deficit as predictors are presented in Figure 2. The model examining TSH versus HAZ showed a low explanatory power ($R^2 = 0.177$; deviance explained = 21%) and no significant association (*edf* = 1, $F = 0.797$, $p = 0.376$) (Table 5). Similarly, FT4 versus HAZ yielded a non-significant result ($p = 0.943$) with minimal deviance explained (19.7%). For height deficit, the model for TSH showed a potential non-linearity (*edf* = 1.63), but remained statistically non-significant ($F = 1.28$, $p = 0.255$). Nevertheless, the model explained 61.5% of the deviance with an R^2 of 0.593. FT4 versus height deficit also showed a high proportion of deviance explained (58.6%), yet the association was not significant ($p = 0.884$) (Table 5).

Table 5. Results of GAM analysis with various models

Model	*edf*	*F*	*p*-value	R^2	Deviance explained (%)
TSH vs HAZ	1	0.797	0.376	0.177	21
FT4 vs HAZ	1	0.005	0.943	0.163	19.7
TSH vs height deficit	1.63	1.28	0.255	0.593	61.5
FT4 vs height deficit	1	0.022	0.884	0.569	58.6

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
JURNAL RAGAM PENGABDIAN - PENELITIAN

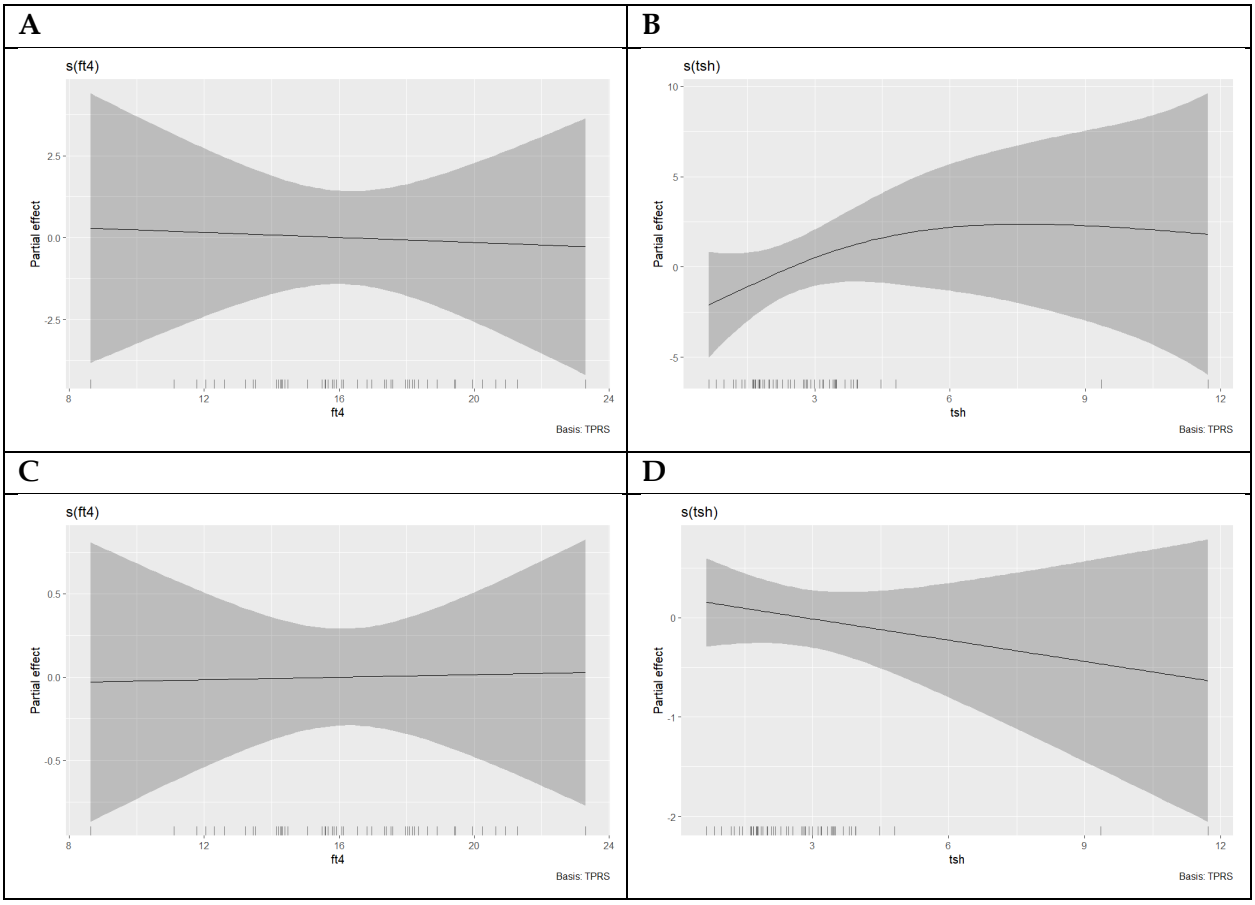


Figure 2. GAM curves for FT4 vs height deficit (a), TSH vs height deficit (b), FT4 vs HAZ (c), and TSH vs HAZ models (d).

Unsupervised Clustering

Unsupervised k-means clustering identified three distinct clusters based on standardized HAZ and height deficit, as presented in Figure 3. Cluster 1 (n = 19) exhibited a mean HAZ of –0.97 and the highest prevalence of height deficit (20.7%), with mean TSH and FT4 levels of 2.88 µIU/mL and 17.30 pmol/L, respectively (Table 6). Cluster 2 (n = 16) had the lowest HAZ (–3.16), height deficit of 17.9%, and the highest TSH level (3.21 µIU/mL). Cluster 3 (n = 16) showed intermediate HAZ (–1.72) but the lowest height deficit (5.82%) and TSH level (2.36 µIU/mL), with a slightly lower FT4 level (15.30 pmol/L) (Table 6).

Between-cluster comparisons for HAZ and height deficit are presented in Table 7. Significant differences are observed in HAZ, with Cluster 2 showing lower HAZ than Cluster 1 (mean difference [MD]: –2.20, 95% CI: –2.78 to –1.61, $p < 0.001$), and Cluster 3 also differing from Clusters 1 and 2 (all $p < 0.01$). For height deficit, Cluster 3 demonstrated significantly lower values compared to both Cluster 1 (MD: –14.86%, 95% CI: –18.64 to –11.09, $p < 0.001$) and Cluster 2 (MD: –12.06%, 95% CI: –16.00 to –8.13, $p < 0.001$), while the difference between Clusters 1 and 2 was not

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
JURNAL RAGAM PENGABDIAN - PENELITIAN

statistically significant (p = 0.183). Analysis of variance indicated no statistically significant differences in TSH or FT4 levels across clusters (ANOVA p = 0.438 and 0.114, respectively). Given that TSH violated the assumption of normality, Kruskal-Wallis tests were also conducted and confirmed the absence of significant clustering effects (TSH: p = 0.479; FT4: p = 0.096).

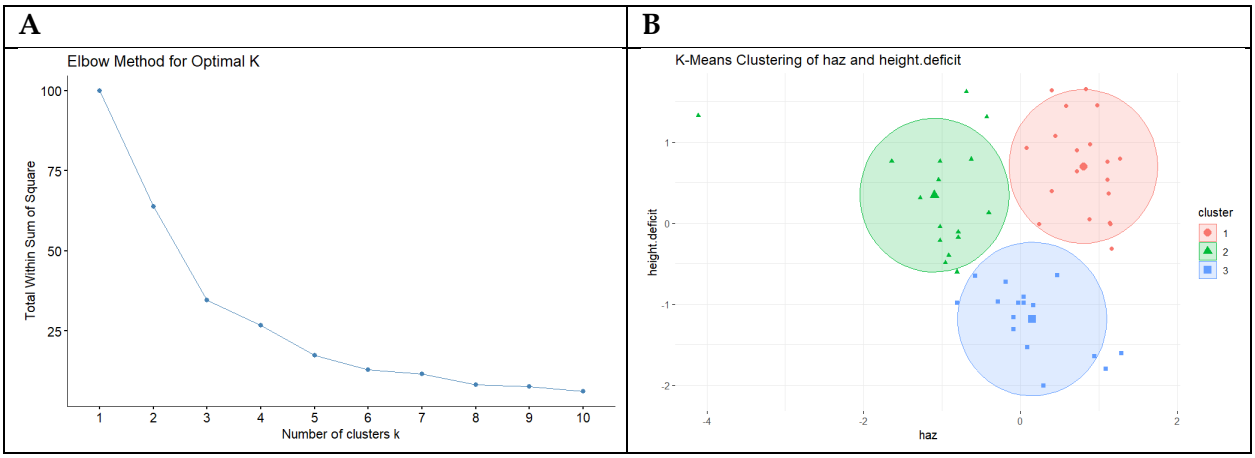


Figure 3. Elbow plot (a) and cluster visualization (b) from unsupervised k-means clustering analysis. Optimal number of clusters was identified as three using the elbow method. K-means clustering of standardized HAZ and height deficit revealed three distinct clusters.

Table 6. Values of the variable of interest in each cluster

Cluster	Height-for-age Z-score	Height deficit (%)	TSH	FT4	n
1	-0.967	20.7	2.88	17.30	19
2	-3.16	17.9	3.21	15.80	16
3	-1.72	5.82	2.36	15.30	16

FT4: Free thyroxine; TSH, thyroid-stimulating hormone

Table 7. Comparisons of HAZ and height deficit between clusters

Comparison	Mean difference	95%CI	p-value
Height-for-age Z-score			
Cluster 2 vs 1	-2.2	-2.78 to -1.61	<0.001
Cluster 3 vs 1	-0.75	-1.34 to -0.17	0.008
Cluster 3 vs 2	1.44	0.84 to 2.05	<0.001
Height deficit			
Cluster 2 vs 1	-2.8	-6.57 to 0.98	0.183
Cluster 3 vs 1	-14.86	-18.64 to -11.09	<0.001
Cluster 3 vs 2	-12.06	16.00 to -8.13	<0.001

CI: confidence interval

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
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This study comprehensively examined the relationship between thyroid function and linear growth among children with thalassemia-β mayor. The participants had a mean HAZ of -1.89 and a mean height deficit of 15.14%, indicating prevalent growth impairment. Cluster analysis identified three distinct growth phenotypes, yet no significant differences in TSH or FT4 levels were observed between clusters. Correlation analyses revealed no significant associations between thyroid hormone levels and either HAZ or height deficit. Linear regression showed that age and sex, but not thyroid markers, were significant predictors of height deficit. Similarly, neither TSH nor FT4 significantly predicted HAZ. Non-linear modeling with GAMs and LOESS confirmed the absence of meaningful curvilinear or threshold effects, with low explanatory power.

Despite thyroid hormone levels falling within normal reference ranges, the persistence of stunting suggests that growth failure in thalassemia is likely multifactorial. While iron overload is widely hypothesized to affect the hypothalamic–pituitary–thyroid (HPT) axis, the absence of a strong correlation in this study implies that other mechanisms (Akıncı et al., 2023; Savvidis et al., 2024). As highlighted previously, endocrine abnormalities in β-thalassemia remain common despite advances in transfusion and chelation therapy, and are influenced by a complex interplay of factors including genotype, liver disease, splenectomy, socioeconomic status, chelation regimen, and micronutrient deficiencies (Venou et al., 2024). For instance, such as chronic anemia, micronutrient deficiencies, delayed puberty, or disruption in the GH–IGF-1 axis may play a more central role (Ashraf et al., 2017; Tenuta et al., 2024). Prior work has shown that growth hormone resistance and hypogonadism are frequent in this population and could underlie the observed anthropometric deficits (Carsote et al., 2022; Ghassemi et al., 2024; Mahwi et al., 2023).

Although some children in this study exhibited subclinical hypothyroidism, the majority had thyroid hormone levels within the normal range. Nonetheless, many of these children still experienced moderate to severe growth failure, reinforcing the notion that thyroid dysfunction is not always the primary determinant of impaired growth in thalassemia. Factors like iron overload, chronic anemia, hypoxia, and their interplay could underlie the broader spectrum of endocrinopathies in this population (Venou et al., 2024). The regression analysis highlighted that older age and male sex were significantly associated with greater height deficits, suggesting that cumulative disease burden and delayed puberty may contribute more prominently to growth impairment. While GAMs explained a considerable proportion of variance after adjusting for age and sex, the thyroid parameters themselves did not significantly influence the models. In a previous report, hypogonadism was found to impair glucose metabolism, and even rare adrenal insufficiency can markedly compromise quality of life in thalassemia (Mattia et al., 2021). Similarly, Ghassemi et al. (2024) provided structured guidance for monitoring growth velocity and managing pubertal disorders in transfusion-dependent thalassemia, recommending proactive, multidisciplinary interventions—including hormone therapy and specialized referral—to optimize developmental outcomes and standardize care.

eISSN 3063-802X & pISSN 3063-8011
JURAGAN
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In clinical practice, our findings support the need for a broader evaluation of growth failure in pediatric thalassemia-β major. Although screening for thyroid dysfunction remains an essential part of routine care, this study found no significant association between thyroid hormone levels and linear growth, suggesting that thyroid hormones may not serve as sensitive markers for early detection of growth impairment. Comprehensive monitoring of growth trajectories, pubertal development, nutritional intake, and iron overload status should remain central in clinical management. However, due to the limited scope of hormonal evaluation in the present study, we cannot make firm recommendations regarding surveillance of other endocrine axes such as GH–IGF-1, adrenal, or gonadal function. These aspects warrant further investigation in future research. In this regard, a guideline has highlighted the importance of structured, proactive monitoring of growth and puberty, with tailored referral and therapeutic strategies to optimize outcomes and standardize care in transfusion-dependent thalassemia (Ghassemi et al., 2024).

The strength of this present study is the use of a multimethod analytical framework, incorporating linear regression, non-linear modeling (GAM and LOESS), and unsupervised clustering, providing a thorough assessment in examining the relationship between thyroid function and growth patterns. However, we acknowledge the limitation of this study in being unable to recruit a larger sample size, thereby restricting statistical power and limiting the generalizability of the findings. Moreover, the cross-sectional design does not allow for causal inference or assessment of longitudinal thyroid–growth dynamics. Confounding factors such as nutritional status, pubertal stage, and iron overload were also not accounted for. In addition, only TSH and FT4 were assessed, without inclusion of other relevant endocrine or metabolic markers.

Clinical Complications and Recommendations for Evaluation and Therapy in Patients with Transfusion-Dependent Thalassemia

Delayed puberty and hypogonadism are among the most common clinical complications resulting from hemosiderosis in patients with transfusion-dependent thalassemia (TDT). Hemosiderosis occurs due to excessive iron accumulation in the body as a consequence of repeated blood transfusions, which can impair the function of multiple organs, including endocrine glands. This condition primarily affects the pituitary gland and gonads, leading to delayed puberty and impaired sexual development (De Sanctis et al., 2019; Faranoush et al., 2023; Farmakis et al., 2022).

To ensure the effectiveness of growth hormone (GH) therapy in patients with TDT, comprehensive and continuous monitoring and evaluation are essential. Growth velocity and insulin-like growth factor-1 (IGF-1) levels should be monitored every three months to assess the patient's response to therapy. In addition, the GH dose should be adjusted based on IGF-1 levels, individual growth response, and relevant growth prediction models. Bone age evaluation should also be performed annually using radiological assessment to evaluate skeletal maturation and

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JURAGAN
JURNAL RAGAM PENGABDIAN - PENELITIAN

determine whether bone development corresponds with the patient's chronological age (Ngim et al., 2017; Farmakis et al., 2022).

Other endocrine functions, including thyroid and adrenal function, should be routinely evaluated before and after initiating growth hormone therapy. This is particularly important because patients with TDT are at high risk of developing pituitary hormone dysfunction due to iron overload. Furthermore, fasting blood glucose levels should be assessed periodically before and during GH therapy, as this treatment may increase insulin resistance and elevate the risk of developing type 2 diabetes mellitus (Farmakis et al., 2022; Ngim et al., 2017).

To comprehensively assess thyroid function, serum levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) should be measured. In addition, evaluation of mineral metabolism and bone health is essential and can be performed by measuring serum levels of total calcium, ionized calcium, inorganic phosphate, magnesium, and alkaline phosphatase. Radiographic examination of the wrist and hand is recommended to determine bone age and assess skeletal development. If abnormal growth velocity is detected, two growth hormone provocation tests are recommended to accurately assess GH secretory capacity (Asad et al., 2016; Farmakis et al., 2022; Ngim et al., 2017).

In addition to hormonal therapy, proper blood transfusion management and iron level control are critical components of care in patients with TDT. Blood transfusions should be administered appropriately and regularly to maintain hemoglobin levels above 9 g/dL in order to support optimal growth and prevent complications associated with chronic anemia. Iron chelation therapy should also be administered correctly to prevent iron overload, with the goal of maintaining serum ferritin levels below 1000 ng/mL. The use of newer-generation iron chelators with fewer skeletal side effects is strongly recommended to improve treatment outcomes and minimize long-term complications (Shah et al., 2010; Cianciulli, 2009; Farmakis et al., 2022).

In addition, the patient's nutritional status must be carefully monitored. Nutritional imbalances should be promptly identified and corrected, as adequate nutrition plays a crucial role in supporting growth, enhancing treatment effectiveness, and maintaining overall health. A comprehensive care approach—including hormonal monitoring, transfusion management, iron chelation therapy, and optimization of nutritional status—is essential to improve quality of life and clinical outcomes in patients with transfusion-dependent thalassemia (Faranoush et al., 2023; Farmakis et al., 2022).

CONCLUSSION AND SUGESTIONS

No significant associations were found between thyroid hormone levels and linear growth indicators in pediatric thalassemia, as assessed using linear, nonlinear, and clustering-based approaches. These findings suggest that thyroid function alone may not explain growth deficits in this population, highlighting the need to explore other contributing factors.

This study showed that Thyroid Stimulating Hormone and Free Thyroxine levels were not significantly associated with linear growth impairment in children with beta-thalassemia major. These findings suggest that growth impairment in this population is likely multifactorial and not solely influenced by thyroid function. Therefore, regular growth monitoring and comprehensive endocrine evaluation remain essential, and further longitudinal studies with broader assessment of clinical and hormonal factors are recommended to support early detection and more effective intervention strategies.

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