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DETERMINANTS OF SHORT STATURE IN CHILDREN WITH TRANSFUSION-DEPENDENT THALASSEMIA: A CROSS-SECTIONAL STUDY IN INDONESIA

Determinan Perawakan Pendek pada Anak dengan Thalassemia Bergantung Transfusi: Studi Potong Lintang di Indonesia

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ABSTRACT

Thalassemia-related iron overload and malnutrition contribute substantially to growth impairment among children with transfusion-dependent thalassemia (TDT). This study aimed to analyze the prevalence and determinants of short stature in pediatric TDT patients. A cross-sectional study was conducted among 120 children aged 24–216 months at Dr. Cipto Mangunkusumo Hospital, Jakarta, between August and December 2023 using consecutive sampling. Nutritional status was assessed using height-for-age and mid-upper arm circumference (MUAC) Z-scores based on WHO standards. Clinical data, including pre-transfusion hemoglobin and serum ferritin levels, were obtained from medical records. Statistical analyses included Chi-square and multivariate logistic regression tests. The prevalence of short stature was 39.2%, while malnutrition prevalence reached 56.7%. Multivariate analysis demonstrated that malnutrition based on MUAC (OR=5.02; 95% CI:1.88–13.44; p=0.001), transfusion frequency ≥2 weeks (OR=3.59; 95% CI:1.40–9.21; p=0.008), and serum ferritin ≥3500 µg/L (OR=3.55; 95% CI:1.22–10.34; p=0.020) were independently associated with short stature. Malnutrition, intensive transfusion frequency, and iron overload were identified as significant determinants of short stature among children with TDT. Routine nutritional assessment using MUAC and optimal iron chelation management should be integrated into thalassemia care to prevent growth impairment.

Keywords: thalassemia, short stature, ferritin, malnutrition, growth failure

ABSTRAK

Kelebihan zat besi dan malnutrisi terkait talasemia memberikan kontribusi besar terhadap gangguan pertumbuhan pada anak-anak dengan talasemia yang membutuhkan transfusi (TDT). Studi ini bertujuan untuk menganalisis prevalensi dan faktor penentu perawakan pendek pada pasien TDT anak. Studi potong lintang dilakukan pada 120 anak berusia 24–216 bulan di Rumah Sakit Dr. Cipto Mangunkusumo, Jakarta, antara Agustus dan Desember 2023 menggunakan pengambilan sampel berurutan. Status gizi dinilai menggunakan skor Z tinggi badan menurut usia dan lingkar lengan atas (MUAC) berdasarkan standar WHO. Data klinis, termasuk kadar hemoglobin dan feritin serum sebelum transfusi, diperoleh dari rekam medis. Analisis statistik meliputi uji Chi-square dan regresi logistik multivariat. Prevalensi perawakan pendek adalah 39,2%, sedangkan prevalensi malnutrisi mencapai 56,7%. Analisis multivariat menunjukkan bahwa malnutrisi berdasarkan MUAC (OR=5,02; 95% CI:1,88–13,44; p=0,001), frekuensi transfusi ≥2 minggu (OR=3,59; 95% CI:1,40–9,21; p=0,008), dan feritin serum ≥3500 µg/L (OR=3,55; 95% CI:1,22–10,34; p=0,020) secara independen berhubungan dengan perawakan pendek. Malnutrisi, frekuensi transfusi intensif, dan kelebihan zat besi diidentifikasi sebagai penentu signifikan perawakan pendek di antara anak-anak dengan TDT. Penilaian nutrisi rutin menggunakan MUAC dan manajemen khelasi zat besi yang optimal harus diintegrasikan ke dalam perawatan talasemia untuk mencegah gangguan pertumbuhan.

Kata kunci: talasemia, perawakan pendek, feritin, malnutrisi, gangguan pertumbuhan

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INTRODUCTION

Among inherited blood disorders, thalassemia stands out as the most prevalent. It results from defective genes responsible for globin protein synthesis, leading to irregularities in hemoglobin production and chronic anemia.[1–3] Clinically, thalassemia is characterized by an imbalance in globin-chain accumulation, ineffective erythropoiesis, increased intestinal iron absorption, and subsequent multimorbidity.[4–7] Children with thalassemia who require regular blood transfusions inevitably experience systemic iron overload. This excess iron causes ferritin to accumulate in vital organs, including the liver, heart, and endocrine glands, which significantly contributes to growth failure manifested as short stature.[8–10]

Short stature in children affected by thalassemia has been widely associated with iron accumulation, the intensive use of iron chelators, and gonadal damage.[11,12] Existing literature indicates that the prevalence of short stature among individuals with thalassemia varies between 30 percent and 50 percent.[13] Furthermore, comorbid malnutrition in this pediatric population frequently exacerbates growth retardation. This is driven by multifactorial causes, primarily substantially increased energy requirements,[14,15] children with thalassemia require 130–150 percent of the recommended daily calorie intake based on age and sex.[16] The insufficient consumption of key micronutrients, such as zinc, folic acid, vitamin D, carotenoids, and retinol-binding protein, further compounds this impaired growth.[17–19]

In Indonesia, thalassemia has emerged as a critical public health challenge, with carrier prevalence estimated at 3–10 percent of the population and a steadily increasing number of transfusion-dependent patients each year.[20] This condition imposes not only a severe clinical burden but also substantial socio-economic challenges due to the escalating demand for lifelong blood transfusions and chelation therapy. Despite this growing magnitude, comprehensive data regarding the specific determinants of growth retardation in the Indonesian pediatric population remains conspicuously scarce. Previous studies have reported inconsistent findings regarding the dominant determinants of short stature in transfusion-dependent thalassemia, particularly concerning the relative contributions of nutritional status, transfusion intensity, and iron overload. Furthermore, evidence from Indonesia remains limited. Specifically, the complex interplay between iron overload markers (serum ferritin), transfusion frequency, and precise nutritional indicators such as mid-upper arm circumference (MUAC) has not been comprehensively evaluated in this demographic.

This persistent knowledge gap creates a significant clinical problem, as current nutritional interventions and transfusion practices risk being contextually suboptimal for local patients, potentially leading to preventable growth faltering. Therefore, this study aimed to determine the prevalence and identify factors associated with short stature among children with transfusion-dependent thalassemia in Indonesia.

METHODS

Study Design and Participants

This analytical observational study with a cross-sectional design involved 120 children with transfusion-dependent thalassemia, aged 24 to 216 months. Data collection was conducted at the Blood Transfusion Unit and the Thalassemia Outpatient Clinic of Dr. Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia, from August to December 2023. Inclusion criteria comprised pediatric patients (aged 24–216 months) receiving regular blood transfusions, operationally defined as requiring a transfusion every 2 to 4 weeks. Exclusion criteria included patients with other chronic or congenital comorbidities, as well as those who had undergone a bone marrow transplantation or splenectomy. Participants were recruited using a consecutive sampling technique, a non-probability method wherein every patient meeting the inclusion criteria during the study period was sequentially enrolled until the minimum sample size was achieved. The study protocol received ethical approval from the Ethics Committee of the Faculty of Medicine, University of Indonesia (Approval Number: KET-875/UN2.F1/ETIK/PPM.00.02/2023). Written informed consent was obtained from the parents or legal guardians of the participants prior to data collection.

Anthropometric Measurements and Clinical Data

Anthropometric measurements were performed in accordance with international guidelines.[21] Height was measured using a Seca Type 217 stadiometer, MUAC was measured using a Seca Type 201 measuring tape. Nutritional status was classified using Z-score categories: height-for-age was determined using WHO Anthro and WHO AnthroPlus software, whereas MUAC Z-scores were categorized using WHO Anthro and PediTools. Short stature was defined as a Z-score between <-2 and -3 standard deviations (SD), and malnutrition (underweight) was defined as a MUAC Z-score between -1 and <-3 SD. Additionally, secondary data, including the mean pre-transfusion Hb concentration and serum ferritin levels over the preceding three months, were extracted from the medical records and laboratory data.

Statistical Analysis

Data management and analysis were performed using IBM SPSS Statistics version 27. The Chi-square test was utilized to assess bivariate associations for qualitative data. Independent variables that demonstrated a p-value <0.25 in the bivariate analysis were subsequently entered into a multivariate logistic regression model to identify the independent determinants of short stature. Variables with p<0.25 in bivariate analysis were included in multivariate logistic regression using the backward stepwise method. The results of the multivariate analysis were presented as Odds Ratios (OR) with 95 percent Confidence Intervals (CI), with statistical significance $p < 0.05$.

RESULTS

This study involved 120 children with transfusion-dependent thalassemia, exhibiting a diverse range of demographic and clinical characteristics as summarized in Table 1.

Table 1
Characteristics of Variables

Variable	n	%
Sex		
Male	65	54.2
Female	55	45.8
Age group (months)		
24 – 59	11	9.2
60 – 143	67	55.8
144 – 216	42	35.0
Hb level before transfusion		
≥ 9 g/dl	53	44.2
< 9 g/dl	67	55.8
Frequency of Blood Transfusion		
Less than every two weeks	57	47.5
Every two weeks or more	63	52.5
Age at first diagnosis (months)		
< 24	38	31.7
6 – 24	65	54.2
< 24	17	14.1
Ferritin then level		
< 3500 µg/dl	41	34.2
≥ 3500 µg/dl	79	65.8
Height for age		
Normal	73	60.8
Short stature	47	39.2
MUAC		
Normal	52	43.3
Malnutrition	68	56.7

Table 2
Bivariate and Multivariate Analysis Results on Risk Factors Contributing to Short Stature in Children with Thalassemia

Characteristic	Bivariate		Multivariate	
	OR	*p-value*	OR	*p-value*
MUAC				
Normal	1		1	
Malnutrition	5.04 (1.70 – 14.94)	0.003	5.02 (1.88 – 13.44)	0.001
Frequency of blood Transfusion				
Less than every two weeks	1		1	
Every two weeks or more	3.43 (1.30 – 9.07)	0.013	3.59 (1.40 – 9.21)	0.008
Hb level before transfusion				
≥ 9 g/dl	1			
< 9 g/dl	1.14 (0.41 – 3.11)	0.795	-	-
Ferritin level				
< 3500 µg/L	1		1	
≥ 3500 µg/L	3.20 (1.07 – 0.59)	0.037	3.55 (1.22 – 10.34)	0.020
Age at first diagnosed (months)				
6 – 24	1			
> 24	0.65 (0.23 – 1.79)	0.407	-	-
Age group (months)				
24 – 144	1			
> 144	1.02 (0.36 – 2.88)	0.967	-	-

The majority of subjects were male, accounting for 65 children (54.2%), while the remaining 55 were female (45.8%). Regarding age distribution, the largest proportion of subjects fell within the 60 to 143-month range (55.8%), followed by the 144 to 216-month group (35.0%). For age at initial diagnosis, the highest prevalence was observed in the 6 to 24-month category, involving 65 children (54.2%). These data indicate that most patients were diagnosed at an early age and were in an active growth phase during the study period.

Regarding clinical management, the results in Table 1 reveal a significant transfusion burden and iron accumulation within the study population. A total of 67 children (55.8%) maintained low pre-transfusion hemoglobin levels, specifically below 9 g/dl. Transfusion frequency was notably intensive, with 63 patients (52.5%) receiving blood every two weeks or more frequently. This condition correlates with high serum ferritin levels, where the majority of subjects (65.8%) presented with levels of 3500 µg/L. Such elevated ferritin levels reflect systemic iron overload, which poses a risk of damaging endocrine organs and impairing linear growth. The evaluation of growth and nutritional status in Table 1 identifies a high prevalence of impairment among children with thalassemia. The prevalence of short stature in this study reached 39.2 percent, affecting 47 out of 120 subjects. In addition to height-related growth failure, nutritional status measured by MUAC also showed concerning results. Sixty-eight children (56.7%) were categorized as malnourished based on MUAC indicators. These findings confirm that undernutrition and growth retardation are highly prevalent complications among thalassemia patients in Indonesia.

Bivariate analysis, as detailed in Table 2, was conducted to identify factors significantly associated with the incidence of short stature. The results indicate that malnutrition (based on MUAC) has a strong association with the risk of short stature, with an OR of 5.04 (p=0.003). Additionally, a transfusion frequency of every two weeks or more was statistically significant with an OR of 3.43 (p=0.013). Serum ferritin levels 3500 µg/L also showed a meaningful association with an OR of 3.20 (p=0.037). Conversely, variables such as pre-transfusion Hb levels, age at diagnosis, and age group did not demonstrate statistical significance in this bivariate analysis.

In the final stage, a multivariate analysis was performed to determine the strongest independent

determinants of growth status, as shown in Table 2. Malnutrition (MUAC) was identified as the most dominant risk factor with an OR of 5.02 (p=0.001), suggesting that malnourished children are five times more likely to experience short stature. Intensive transfusion frequency remained a significant determinant with an OR of 3.59 (p=0.008). Similarly, high serum ferritin levels (3500 µg/L) yielded an OR of 3.55 (p=0.020). Overall, these results emphasize that targeted nutritional interventions and stringent iron load control are crucial for preventing stunting in children with thalassemia

DISCCUSSION

This cross-sectional study reinforces the growing body of evidence indicating a substantial burden of growth failure among pediatric patients with transfusion-dependent thalassemia. The study identified a high prevalence of short stature (39.2%) occurring concurrently with severe malnutrition (56.7%), underscoring the magnitude of growth impairment in this population. By analyzing multiple anthropometric and clinical parameters, the study addresses a critical epidemiological question regarding the primary pathophysiological determinants of stunting in resource-limited settings. In such contexts, constraints in medical infrastructure and nutritional support significantly influence the clinical trajectory of chronic genetic disorders. The statistical analysis specifically revealed that severe malnutrition, as measured by mid-upper arm circumference (MUAC), emerged as the strongest independent predictor of short stature, with an odds ratio of 5.02 (1.88–13.44), far exceeding the influence of other variables.[22] These findings highlight the urgent need to prioritize nutritional assessment and intervention as core components of thalassemia management.

Given the dominant role of severe malnutrition in the development of short stature, conventional anthropometric methods that rely heavily on body weight and body mass index (BMI) require critical reevaluation.[23] In pediatric thalassemia patients, these traditional indicators are substantially biased due to the high prevalence of massive hepatosplenomegaly resulting from extramedullary hematopoiesis. This organ enlargement creates an artificial increase in body weight, often masking severe skeletal muscle wasting and depletion of subcutaneous adipose tissue.[24] As a result, weight-based indices frequently fail to detect underlying protein-energy malnutrition. MUAC, in contrast, has demonstrated superior accuracy because it directly reflects peripheral muscle and fat stores that are unaffected by visceral organ enlargement.[23] The study's findings therefore support the integration of MUAC as a primary anthropometric indicator in clinical protocols for thalassemia care.

The striking dominance of severe malnutrition as the strongest independent determinant of short stature necessitates an immediate and critical reassessment of the anthropometric methodologies routinely used in pediatric hematology and oncology settings worldwide. Traditional growth indices particularly body weight and BMI are profoundly confounded and rendered unreliable in thalassemia due to pervasive hepatosplenomegaly. This extreme intra-abdominal organomegaly, driven by relentless extramedullary hematopoiesis and chronic reticuloendothelial congestion, artificially inflates total body mass and produces deceptively normal nutritional parameters. Consequently, reliance on weight-based metrics dangerously obscures the progression of severe muscle wasting and rapid depletion of subcutaneous fat, leading to a substantial underestimation of critical protein-energy malnutrition. In contrast, MUAC emerges as a far more accurate and unbiased surrogate for true nutritional status because it isolates peripheral skeletal muscle and fat reserves from central weight distortions. The markedly elevated odds ratio associated with reduced MUAC in this cohort underscores the causal link between peripheral tissue catabolism and impaired linear growth, validating MUAC as an indispensable clinical tool.[14,25]

The profound degree of peripheral wasting observed in these vulnerable children is intrinsically linked to a chronic hypermetabolic state driven by ineffective erythropoiesis. This pathological process, characterized by accelerated apoptosis of abnormal erythroid precursors within the bone marrow, consumes an exceptionally high amount of metabolic energy. To sustain basic physiological functions while supporting this hyperactive yet ineffective hematopoietic system, affected children require caloric intake equivalent to 130–150 percent of

the standard recommended daily allowance. In resource-limited settings such as Indonesia, achieving this elevated caloric threshold is extremely challenging due to food insecurity and limited dietary diversity. As a result, children experience persistent negative energy balance, forcing the body to divert available nutrients away from growth processes toward essential survival functions. Over time, this metabolic prioritization leads to progressive muscle wasting and irreversible deceleration of bone elongation, ultimately manifesting as permanent stunting.[26]

The chronic nutritional deficit induced by this hypermetabolic state exerts a direct and catastrophic impact on the cellular dynamics of the epiphyseal growth plates. Longitudinal bone growth depends on continuous, energy-intensive proliferation and hypertrophic differentiation of chondrocytes within the growth plate. Under severe protein-energy malnutrition reflected by markedly reduced MUAC circulating levels of essential osteogenic nutrients such as amino acids, zinc, and active vitamin D fall below critical thresholds. Simultaneously, prolonged energy deprivation suppresses key anabolic signaling pathways, including the mammalian target of rapamycin (mTOR) pathway, which is essential for cellular growth and division.[27] This suppression induces premature senescence of progenitor stem cells in the resting zone of the growth plate and thinning of the proliferative zone, ultimately extinguishing the bone's capacity for elongation. The strong statistical association between MUAC-defined malnutrition and short stature therefore reflects a profound biological failure in which skeletal maturation is sacrificed to sustain basic metabolic demands.[28]

Beyond nutritional deficits, this study also identifies severe systemic iron overload indicated by serum ferritin levels exceeding 3500 µg/L as a major independent determinant of growth failure. Chronic transfusions, in the absence of physiological mechanisms for iron excretion, lead to the accumulation of toxic non-transferrin-bound iron in vital organs. The anterior pituitary gland is particularly vulnerable to this deposition, as free iron readily crosses the blood–brain barrier and infiltrates somatotroph cells responsible for growth hormone (GH) synthesis. Within these cells, iron triggers intense oxidative stress, mitochondrial damage, and apoptosis, resulting in diminished GH production. Reduced GH subsequently leads to decreased hepatic synthesis of insulin-like growth factor 1 (IGF-1), a critical mediator of linear growth. Thus, extreme hyperferritinemia directly disrupts the GH–IGF-1 axis, contributing significantly to impaired growth.[29,30]

The downstream consequences of pituitary iron toxicity include profound disruption of the GH–IGF-1 axis, which serves as the central endocrine driver of somatic growth. IGF-1 is essential for chondrocyte proliferation and hypertrophy, and its deficiency results in markedly reduced height velocity. Additionally, iron deposition in the liver induces inflammation and GH resistance, further impairing IGF-1 production even when residual GH secretion persists.[31] This dual-hit mechanism central GH deficiency combined with peripheral hepatic resistance effectively deprives the growth plates of necessary trophic signals. As a result, endochondral ossification stalls, and children fail to achieve normal linear growth. The strong association between hyperferritinemia and short stature observed in this study therefore reflects severe neuroendocrine dysfunction arising from inadequate iron chelation.[32]

Another compelling finding is that high transfusion frequency defined as every two weeks or more emerged as an independent risk factor for short stature. Although frequent transfusions are intended to suppress ineffective erythropoiesis and improve oxygen delivery, the study reveals a paradoxical association with impaired growth. Each transfusion introduces approximately 200–250 mg of iron, and without optimal chelation, the rate of iron accumulation rapidly exceeds the body's capacity for clearance. This accelerated iron loading overwhelms chelation therapy, leading to early and severe tissue siderosis. Frequent transfusions "increase the risk of growth impairment," highlighting the need for individualized transfusion strategies that balance hematologic benefits with the risks of iron toxicity.[33]

Despite its robust findings, this study has several limitations that warrant consideration. The cross-sectional design precludes establishing temporal causality between nutritional status, iron overload, and growth outcomes. The reliance on secondary clinical data for hemoglobin and ferritin introduces potential information bias due to variability in laboratory methods or documentation. The

absence of endocrine biomarkers such as IGF-1 or GH stimulation tests limits the ability to directly confirm the proposed mechanistic pathways. Additionally, the study was conducted at a single national referral hospital, which may limit generalizability to broader populations.[34,35] Nevertheless, the consistency of these findings with international literature strengthens their relevance for clinical practice.

Overall, this study demonstrates that short stature in transfusion-dependent thalassemia arises from a complex interplay of severe malnutrition, hypermetabolism, iron toxicity, and transfusion intensity. MUAC emerges as the most reliable predictor of growth impairment, reflecting true peripheral wasting. Iron overload disrupts the GH–IGF-1 axis and causes irreversible endocrine damage, while frequent transfusions accelerate iron accumulation. These findings underscore the need for revised clinical protocols emphasizing MUAC-based nutritional screening, optimized iron chelation, and individualized transfusion regimens to prevent long-term growth morbidity.

CONCLUSION

This study demonstrates that short stature is a highly prevalent and severe complication among pediatric patients with transfusion-dependent thalassemia, driven by a complex interplay of hypermetabolism, iron toxicity, and intensive transfusion requirements. Notably, severe malnutrition, when accurately evaluated using MUAC, emerges as the most profound independent determinant of growth impairment in this population. Furthermore, the significant independent associations between hyperferritinemia, frequent blood transfusions, and short stature underscore the detrimental impact of unmanaged systemic iron overload on the neuroendocrine axis. Ultimately, these findings indicate that preventing irreversible stunting requires a comprehensive approach that moves beyond isolated hematological management to concurrently address severe peripheral tissue catabolism and optimal iron clearance.

RECOMMENDATIONS

Healthcare providers must prioritize mid-upper arm circumference (MUAC) overweight-based metrics to avoid assessment biases caused by organomegaly, alongside rigorous monitoring of iron chelation therapy. At the policy level, routine MUAC-based nutritional screening and targeted interventions urgently need to be integrated into national standard protocols for thalassemia care. Furthermore, future research should employ longitudinal cohort designs and utilize specific endocrine biomarkers to definitively establish the causal pathways between nutritional deficits, cumulative iron overload, and neuroendocrine dysfunction

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