

Source details

Paediatrica Indonesiana

Open Access ⓘ

Scopus coverage years: from 1964 to 1991, from 2019 to Present

Publisher: Indonesian Society of Pediatrician

ISSN: 0030-9311

Subject area: Medicine: Pediatrics, Perinatology and Child Health

Source type: Journal

CiteScore 2022
0.3

SJR 2022
0.134

SNIP 2022
0.129

[View all documents >](#) [Set document alert](#) [Save to source list](#) [Source Homepage](#)

[CiteScore](#) [CiteScore rank & trend](#) [Scopus content coverage](#)

i Improved CiteScore methodology

CiteScore 2022 counts the citations received in 2019-2022 to articles, reviews, conference papers, book chapters and data papers published in 2019-2022, and divides this by the number of publications published in 2019-2022. [Learn more >](#)

CiteScore 2022 ▼

$$0.3 = \frac{76 \text{ Citations 2019 - 2022}}{221 \text{ Documents 2019 - 2022}}$$

Calculated on 05 May, 2023

CiteScoreTracker 2023 ⓘ

$$0.3 = \frac{55 \text{ Citations to date}}{180 \text{ Documents to date}}$$

Last updated on 05 May, 2023 • Updated monthly

CiteScore rank 2022 ⓘ

Category	Rank	Percentile
Medicine		
└ Pediatrics, Perinatology and Child Health	#260/306	15th

[View CiteScore methodology >](#) [CiteScore FAQ >](#) [Add CiteScore to your site ↗](#)



SJR

Scimago Journal & Country Rank

Enter Journal Title, ISSN or Publisher Name

[Home](#)[Journal Rankings](#)[Country Rankings](#)[Viz Tools](#)[Help](#)[About Us](#)

Paediatrica Indonesiana

COUNTRY

[Indonesia](#)Universities
and research
institutions in
IndonesiaMedia Ranking
in Indonesia

SUBJECT AREA AND CATEGORY

[Medicine](#)
[Pediatrics,](#)
[Perinatology and](#)
[Child Health](#)

PUBLISHER

[Indonesian Society
of Pediatrician](#)

H-INDEX

3

PUBLICATION TYPE

[Journals](#)

ISSN

00309311

COVERAGE

1964-1991, 2020-
2022

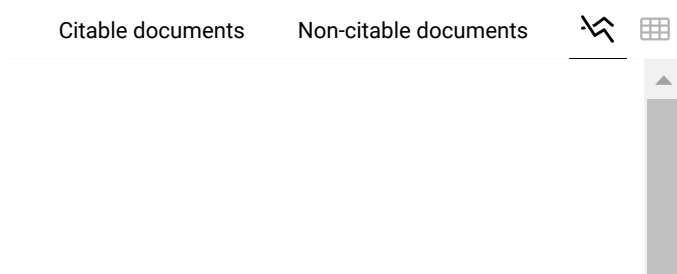
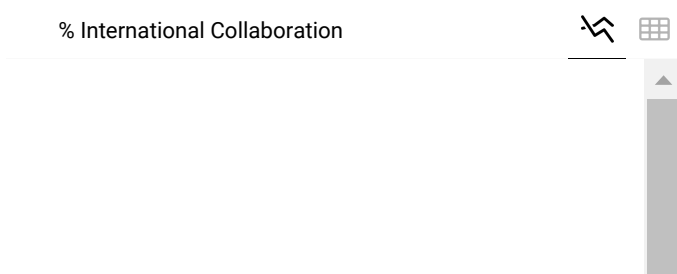
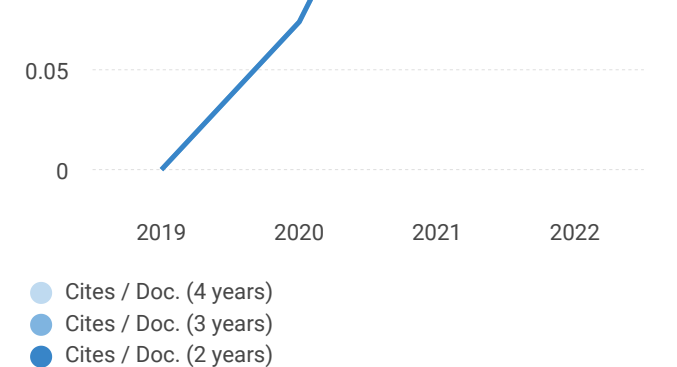
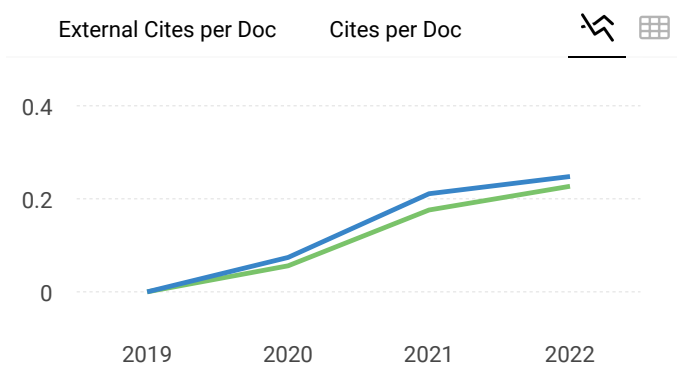
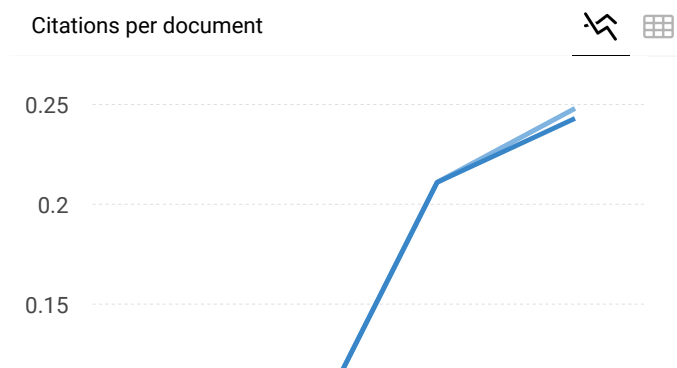
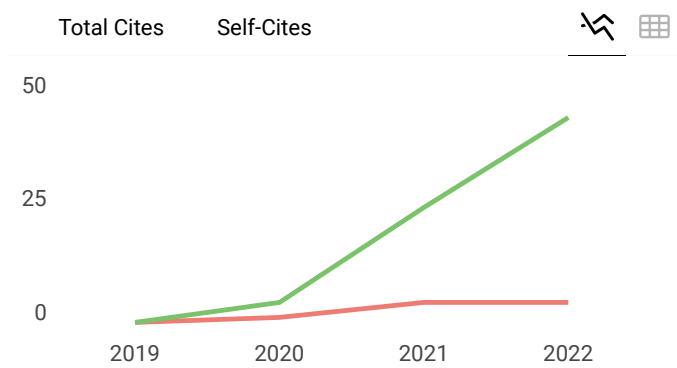
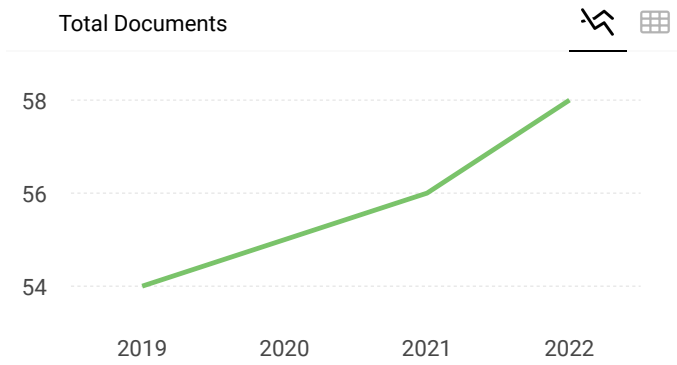
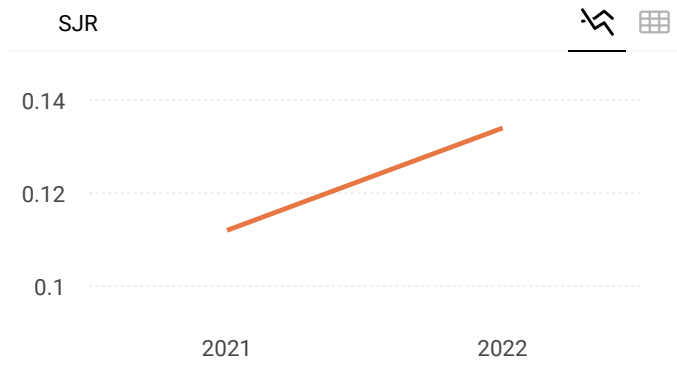
INFORMATION

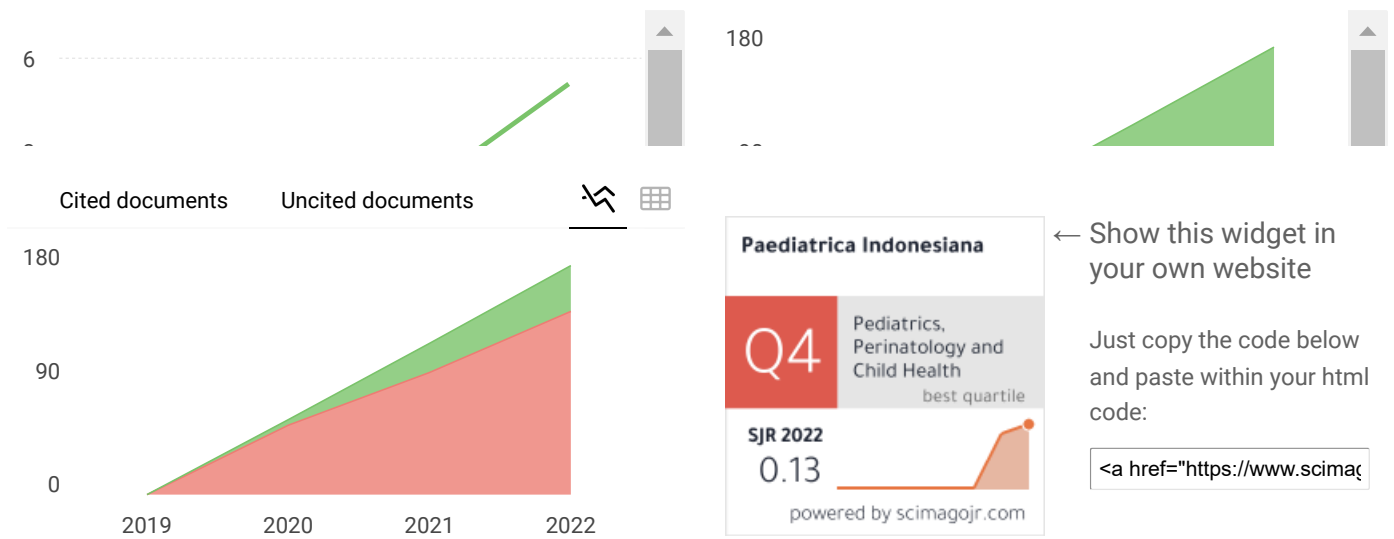
[Homepage](#)[How to publish in
this journal](#)[enquiry@paediatricai
ndonesiana.org](mailto:enquiry@paediatricai
ndonesiana.org)

SCOPE

Paediatrica Indonesiana is an international peer reviewed journal embracing all the scientific, clinical, and public health disciplines that address all aspects of pediatrics and perinatal medicine. It includes articles related to research findings and occasionally case reports and clinical reviews.

[Join the conversation about this journal](#)





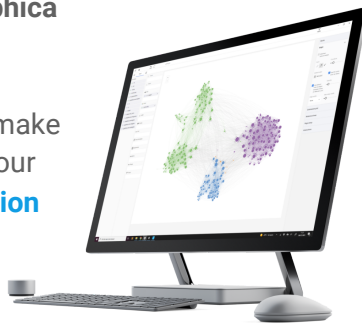
← Show this widget in your own website

Just copy the code below and paste within your html code:

```
<a href="https://www.scimaç
```

SCImago Graphica

Explore, visually communicate and make sense of data with our [new data visualization tool](#).



Metrics based on Scopus® data as of April 2023

Leave a comment

Name

Email

(will not be published)

[CURRENT](#)

[ARCHIVES](#)

[ABOUT](#) ▾

[EDITORIAL BOARD](#)

[PUBLICATION ETHICS & MALPRACTICES](#)

[INSTRUCTIONS TO AUTHOR](#)

[REGISTER](#)

[LOGIN](#)

Editorial Board

Editor-in-Chief

Partini P. Trihono, Pediatric Nephrology, Universitas Indonesia, Jakarta ([Scopus:5](#); [Google Scholar:9](#); ORCID: <https://orcid.org/0000-0003-2893-6049>)

Vice Editor

Amanda Soebadi, Pediatric Neurology, Universitas Indonesia, Jakarta ([Scopus:3](#); [Google Scholar:4](#); ORCID:<https://orcid.org/0000-0001-9424-0029>)

Associate Vice Editor

Fitri Primacakti, Pediatric Hemato-Oncology, Universitas Indonesia, Jakarta ([Scopus:2](#); [Google Scholar:3](#))

Editorial Board

Agustini Utari, Pediatric Endocrinology, Universitas Diponegoro, Semarang ([Scopus:9](#); [Google Scholar:12](#); ORCID:<https://orcid.org/0000-0001-5965-1981>)

Ahmad Suryawan, Developmental Behavioral & Community Pediatrics, Universitas Airlangga ([Scopus:3](#); [Google Scholar:9](#); ORCID: <https://orcid.org/0000-0002-3377-0381>)

Ariani Dewi Widodo, Pediatric Gastrohepatology, Universitas Indonesia, Jakarta ([Scopus:5](#))

Cuno S. P. M. Uiterwaal, University Medical Centre, Utrecht ([Scopus:69](#))

Dominicus Husada, Infection & Tropical Pediatrics, Universitas Airlangga, Surabaya ([Scopus:7](#); [Google Scholar:10](#); ORCID: <https://orcid.org/0000-0001-9191-9546>)

Elisabeth Siti Herini, Pediatric Neurology, Universitas Gadjah Mada, Yogyakarta ([Scopus:6](#); [Google Scholar:10](#))

Finny Fitry Yani, Pediatric Respiriology, Universitas Andalas, Padang ([Scopus:6](#); [Google Scholar:10](#); ORCID:<https://orcid.org/0000-0002-4515-6530>)

Haryanti Fauzia Wulandari, Pediatric Imaging, Universitas Indonesia, Jakarta ([Google Scholar:1](#))

Hasri Samion, Institut Jantung Negara, Kuala Lumpur ([Scopus:12](#))

I Dewa Gede Ugrasena, Pediatric Hemato-Oncology, Universitas Airlangga, Surabaya ([Scopus:3](#); [Google Scholar:7](#))

I Gusti Ayu Trisna Windiani, Developmental Behavioral & Community Pediatrics, Universitas Udayana, Denpasar ([Scopus:7](#); [Google Scholar:8](#))

I Gusti Lanang Sidiartha, Pediatric Nutrition & Metabolic Diseases, Universitas Udayana, Denpasar ([Google Scholar:11](#))

I Gusti Made Reza Gunadi Ranuh, Pediatric Gastrohepatology, Universitas Airlangga, Surabaya ([Google Scholar:12](#))

Indah Kartika Murni, Pediatric Cardiology, Universitas Gadjah Mada, Yogyakarta ([Scopus:9](#); [Google Scholar:12](#))

Inke Nadia Diniyanti Lubis, Infection & Tropical Pediatrics, Universitas Sumatera Utara ([Scopus:9](#); [Scopus:10](#); ORCID: <https://orcid.org/0000-0001-7075-9491>)

Irene Yuniar, Emergency & Pediatric Intensive Care, Universitas Indonesia, Jakarta ([Scopus:1](#); [Google Scholar:4](#))

Jose Batubara, Pediatric Endocrinology, Universitas Indonesia, Jakarta ([Scopus:5](#); [Google Scholar:12](#))

Nadira Rasyid Ridha, Pediatric Hemato-Oncology, Universitas Hasanuddin, Makassar ([Google Scholar:4](#))

Ni Putu Veny Kartika Yantie, Pediatric Cardiology, Universitas Udayana, Denpasar ([Scopus:1](#); [Google Scholar:2](#))

Paul Glasziou, University of Sydney Faculty of Medicine, Queensland ([Scopus:1013](#); [Google Scholar:141](#); ORCID: <https://orcid.org/0000-0001-7564-073X>)

Raden Muhammad Indra, Pediatric Neurology, Universitas Sriwijaya, Palembang ([Scopus:1](#); [Google Scholar:2](#))

Ratno J. M. Sidauruk, Pediatric Imaging, Universitas Indonesia, Jakarta

Reni Ghrahani, Pediatric Allergy Immunology, Universitas Padjadjaran, Bandung ([Scopus:3](#); [Google Scholar:6](#); ORCID: <https://orcid.org/0000-0003-4476-2958>)

Retno Palupi-Baroto, Pediatric Nephrology, Universitas Gadjah Mada, Yogyakarta ([Scopus:3](#); [Google Scholar:3](#); ORCID: <https://orcid.org/0000-0001-8447-8682>)

Rina Triasih, Pediatric Respiriology, Universitas Gadjah Mada, Yogyakarta ([Scopus:15](#), [Google Scholar:20](#); ORCID: <https://orcid.org/0000-0002-6907-3422>)

Ririe Fachrina Malisie, Emergency & Pediatric Intensive Care, Universitas Sumatera Utara, Medan ([Scopus:1](#); [Google Scholar:2](#))

Risky Vitria Prasetyo, Pediatric Nephrology, Universitas Airlangga, Surabaya ([Scopus:3](#); [Google Scholar:4](#); ORCID: <https://orcid.org/0000-0002-1708-5384>)

Rosalina Dewi Roeslani, Neonatology, Universitas Indonesia, Jakarta ([Scopus:3](#); [Google Scholar:5](#))

Stephen M. Graham, Melbourne ([Scopus:52](#); [Google Scholar:78](#))

Sudigdo Sastroasmoro, Pediatric Cardiology, Universitas Indonesia, Jakarta ([Scopus:11](#))

Sumadiono, Pediatric Allergy Immunology, Universitas Gadjah Mada, Yogyakarta ([Scopus:2](#); [Google Scholar:6](#))

Tetty Yuniarti, Neonatology, Universitas Padjadjaran, Bandung

Yoga Devaera, Pediatric Nutrition & Metabolic Diseases, Universitas Indonesia, Jakarta ([Scopus:3](#);

Google [Scholar:7](#); ORCID: <https://orcid.org/0000-0002-5427-9823>)

Yvan Vandenplas, Universitair Ziekenhuis, Brussels ([Scopus:68](#))



MAKE A SUBMISSION



Author Form

Our journal is indexed by:

Scopus®



DOAJ DIRECTORY OF
OPEN ACCESS
JOURNALS



Published by Indonesian Pediatric Society

E-ISSN 2338-476X | P-ISSN 0030-9311



This work is licensed under a [Creative Commons Attribution 4.0 International \(CC BY 4.0\)](https://creativecommons.org/licenses/by/4.0/)

[Web Analytics](#)

Platform &
workflow by
OJS / PKP

LOGIN

HOME / ARCHIVES / Vol 62 No 2 (2022): March 2022



DOI: <https://doi.org/10.14238/pi62.2.2022>

PUBLISHED: 2022-04-18

PEDIATRIC CARDIOLOGY

Factors contributing to successful patent ductus arteriosus closure with first pharmacological course

I Gusti Ayu Made Dwisri Okadharna, Ni Putu Veny Kartika Yantie, Eka Gunawijaya

86-90

PDF

PEDIATRIC ENDOCRINOLOGY

Adherence and growth outcomes in children with growth disorders: results from the Easypod™ Connect Observational Study (ECOS) in Indonesia, Singapore, and Taiwan

Aman Bhakti Pulungan, Fabian Yap, Mei-Chyn Chao, Kah Yin Loke, Chen Yang, Tianrong Ma, Leroy Ovbude, Pen-Hua Su

79-85

PDF

Childhood obesity as a predictor of type 2 diabetes mellitus in adults: a systematic review and meta-analysis

Marco Raditya, Fabiola Cathleen, Daniell Edward Raharjo, Kristian Kurniawan

120-9

PDF

PEDIATRIC HEMATO-ONCOLOGY

Comparative efficacy, safety, and cost of iron chelation monotherapy vs. combination therapy in pediatric beta-thalassemia major: a single-center retrospective study

Dewi Sharon Simorangkir, Nafrialdi Nafrialdi, Pustika Amalia Wahidiyat, Vivian Soetikno

91-7

PDF

Vitamin D, insulin-like growth factor-1, and stunting in children with transfusion-dependent thalassemia

I Gusti Ayu Putu Eka Pratiwi, Roedi Irawan, I Dewa Gede Ugrasena, Muhammad Faizi

98-103

PDF

NEONATOLOGY

Resuscitation of very preterm infants with 30% vs. 50% oxygen: a randomized controlled trial

Risma Karina Kaban, Asril Aminullah, Rinawati Rohsiswatmo, Badriul Hegar, Abdurahman Sukadi, Peter Graham Davis
104-14

 PDF

PEDIATRIC NEUROLOGY

Erasmus Guillain-Barre Syndrome Outcome Score (EGOS) to predict functional outcomes

Maria Ulfa, Titis Widowati, Agung Triono
130-7

 PDF

PEDIATRIC RESPIROLOGY

Exhaled carbon monoxide in children with asthma and allergic rhinitis

Yulia Fatma Wardani, Rina Triasih, Amalia Setyati
115-9

 PDF

CASE REPORT

Growth and development in an extremely low birth weight infant with osteopenia of prematurity: a case report

Syifa Armenda, Tunjung Wibowo, Mei Neni Sitaresmi
143-8

 PDF

Successful treatment of Budd-Chiari Syndrome with Rivaroxaban in a six week old Bangladeshi infant

Mukesh Khadga, Ferdous Ara Begum, Mohammad Wahiduzzaman Mazumder, Mohammad Benzamin, Nazmul Ahamed Rony, Abu Zafor Mohammad Raihanur Rahman, Ayesha Siddiqua, Nazmul Hassan, Abu Sayed Mohammad Bazlul Karim
138-42

 PDF



MAKE A SUBMISSION



Author Form

Our journal is indexed by:

Scopus[®]

Original Article

Vitamin D, insulin-like growth factor-1, and stunting in children with transfusion-dependent thalassemia

I Gusti Ayu Putu Eka Pratiwi, Roedi Irawan, I Dewa Gede Ugrasena,
Muhammad Faizi

Abstract

Background Transfusion-dependent thalassemia (TDT) has a major impact on a child's growth and is associated with stunting, risk of vitamin D deficiency, and decreased insulin-like growth factor-1 (IGF-1). To date, the relationship between vitamin D levels and stunting in TDT remains unclear. Furthermore, the role of vitamin D and IGF-1 in mediating stunting in TDT patients is still unknown.

Objective To investigate the relationship between stunting and vitamin D as well as IGF-1 levels in children with TDT.

Methods This cross-sectional study involved 50 TDT children aged 5 to 18 years, included consecutively from the Pediatric Hemato-oncology Outpatient Clinic, Dr. Soetomo Hospital, Surabaya, East Java. Subjects were divided into two groups: stunted (S) and not stunted (NS). Vitamin D and IGF-1 were evaluated by antibody competitive immunoassay and sandwich-enzyme-linked immunosorbent assay (ELISA), respectively. Age, sex, and duration of repeated transfusion were analyzed as confounding factors.

Results Median IGF-1 levels were 91.43 (13.67-192.86) ng/mL and 161.53 (17.99-363.01) ng/mL in the S and NS groups, respectively ($P=0.011$). Mean vitamin D levels were 20 (+ 5.71) ng/mL and 20.46 (5.25) ng/mL in the S and NS groups, respectively ($P=0.765$). The correlation coefficient (r) of vitamin D and IGF-1 levels was not significant. Multivariate analysis showed that low IGF-1 levels, male, and longer duration of repeated transfusions were associated with stunting in children with TDT.

Conclusion Low IGF-1 level is associated with stunting in children with TDT. Vitamin D is not significantly associated with either stunting or IGF-1 in children with TDT. [Paediatr Indones. 2022;62:98-103; DOI: 10.14238/pi62.1.2022.998-103].

Keywords: transfusion-dependent thalassemia; stunting, IGF-1; vitamin D

Transfusion-dependent thalassemia (TDT) has negative impacts on growth and has been associated with stunting.^{1,2} Prior studies found an increased prevalence of stunting among thalassemic children, varying from 25 to 57.1%, depending on the age and sex.³⁻⁵ Despite the efforts to increase vitamin D levels using supplementation, vitamin D deficiency remains prevalent in thalassemia patients.^{3,6-9}

Insulin-like growth factor-1 (IGF-1) has a substantial role in growth regulation. Calcitriol (1,25-dihydroxy vitamin D₃) increases IGF-1 receptors and, therefore, promotes the action of IGF-1. The IGF-1 stimulates 1 α -hydroxylase and decreases 24-hydroxylase gene expression, causing an increase in calcitriol level. Calcitriol also increases insulin-like growth factor-binding protein-3 (IGFBP-3).¹⁰ There are several mechanisms that may explain the occurrence of stunting in children with thalassemia, one of which is decreased IGF-1 level.¹¹ Low IGF-1 level has

From the Department of Child Health, Universitas Udayana Medical School/Sanglah Hospital, Denpasar, Bali, Indonesia.

Corresponding author: I Gusti Ayu Putu Eka Pratiwi. Department of Child Health, Universitas Udayana Medical School/Sanglah Hospital. Jl. Kesehatan, Denpasar, Bali, Indonesia. +628123920750. gstayu_eka@unud.ac.id.

Submitted July 12, 2020. Accepted March 4, 2022.

been associated with stunting in patients with TDT. However, the relationship between vitamin D levels and stunting in TDT remains unclear. Furthermore, the role of vitamin D and IGF-1 in mediating stunting in TDT patients is still unknown. To the best of our knowledge, no study in Indonesia has investigated the relationship between vitamin D levels and stunting in thalassemia patients.

Methods

This cross-sectional study aimed to explore the relationship between stunting in children with TDT and their vitamin D and IGF-1 levels. This study was approved by the Health Research Ethics Committee, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia, and conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from subjects' parents before the study was conducted. This study was conducted between January and June 2019.

The inclusion criteria were children with TDT aged 5 to 18 years whose parents or guardians consented to participation. Exclusion criteria were patients with familial short stature, and those who received vitamin D supplementation or growth hormone therapy. Subjects were included consecutively from the Hematology Oncology Outpatient Clinic, Pediatrics Department, Dr. Soetomo Hospital. They underwent measurements of anthropometry, vitamin D, and IGF-1 levels. Subjects were divided into two groups: stunted and not stunted. Stunting was defined as height based on age and sex < 3rd percentile according to the 2000 CDC Growth Chart.¹² Malnutrition was defined by mid upper arm circumference less than 85% from median in Frisancho mid upper arm circumference reference based on age and sex.¹³

The minimum required sample size was calculated to be 20 per group, using a formula for hypothesis test for mean difference in two populations ($n = 2\sigma^2(Z_{1-\alpha}/2 + Z_{1-\beta})^2 / (\mu_1 - \mu_2)^2$). This study used $\alpha = 0.05$; 90% power; $\sigma^2 = 1,526.46$.¹⁴ The projected mean IGF-1 difference from two population groups was 40 ng/mL.

Blood specimens (3 mL) were collected for vitamin D and IGF-1 examination and centrifuged. Serum was stored at -80°C prior to analysis. Vitamin

D was evaluated by ADVIA Centaur VitD assay (antibody competitive immunoassay) and IGF-1 was evaluated by sandwich-enzyme-linked immunosorbent assay (ELISA) for human-IGF-1 serum quantitative (ElabscienceR Human IGF-I ELISA Kit Catalog #E-EL-H0086). Vitamin D levels were divided into three categories: deficient (<15 ng/mL), insufficient (15 to <20 ng/mL), and sufficient (20-100 ng/mL).¹⁵

Hemoglobin electrophoresis data and most recent laboratory findings (hemoglobin, blood urea nitrogen (BUN), serum creatinine (SC), aspartate transaminase (AST), alanine transaminase (ALT), and ferritin levels) were obtained from medical records. Glomerular filtration rate (in mL/minute/1.73 m²) was calculated by using Schwartz formula ($k \times \text{height in cms} : \text{SC in mg/dL}$; with $k = 0.55$ for 1 to 13-year-old, $k = 0.7$ for 13 to 21-year-old male, and $k = 0.57$ for 13 to 21-years-old female). Glomerular filtration rate (GFR) was classified as normal (80-175 mL/minute/1.73 m²), decreased (< 80 mL/minute/1.73 m²), and glomerular hyperfiltration (> 175 mL/minute/1.73 m²).¹⁶ Data were analyzed by SPSS 16.0 for Windows software. Subjects' characteristics were analyzed descriptively. Simple logistic regression was used to analyze the relationship between vitamin D levels and stunting, as well as IGF-1 and stunting in children with TDT. Spearman's rank correlation was used to analyze vitamin D and IGF-I levels. Multiple logistic regression (backward Wald method) was used to analyze vitamin D levels, IGF-1 levels, and other variables that could be contributing factors for stunting in children with TDT. Results with P values < 0.05 were considered to be statistically significant.

Results

Of 99 TDT patients screened during this study period, 49 children were excluded because of familial short stature. The 50 included children were divided into stunted (S) or not stunted (NS) groups (25 subjects each). The characteristics of subjects (age, sex, type of thalassemia, type of iron chelator used, current and previous hemoglobin levels, AST levels, ALT levels, glomerular filtration rate, ferritin levels, and transfusion interval) were similar in the S and NS groups (**Table 1**). Malnutrition was more prevalent in the S group compared to the NS group. The duration of

regular transfusion was longer in S group than NS group. The median height based on age and sex were 0.1 (range 0.1-1.36) percentile and 11.7 (range 3.1-55.7) percentile for S and NS groups, respectively.

Mean vitamin D level of all subjects was 20.23 (SD 5.43) ng/mL. Normal vitamin D level was found in 27 patients (54%), insufficient level in 13 patients (26%), and deficient level in 10 (20%) subjects. Mean vitamin D levels were 20.00 (SD 5.71) ng/mL and 20.46

(SD 5.25) ng/mL, in the S and NS groups, respectively. Vitamin D level was not associated with stunting in this study (OR 0.984; 95%CI 0.888 to 1.092; P=0.765).

Median IGF-1 levels were 91.43 (range 13.67-192.86) ng/mL and 161.3 (range 17.99-363.01) ng/mL in the S and NS groups, respectively. Stunting had a significant negative association with IGF-1 (OR 0.992; 95%CI 0.986 to 0.998; P=0.011).

Table 1. Subject characteristics in stunted and not stunted subjects

Characteristics	Stunted (S) (n = 25)	Not stunted (NS) (n = 25)	P value
Mean age (SD), years	12.28 (3.31)	10.98 (3.79)	0.203
Age group, n			
>5 to <12 years	10	16	0.093
12 –18 years	15	9	
Sex, n			
Male	15	16	0.771
Female	10	9	
Malnutrition, n			
Yes	21	12	0.010
No	4	13	
Type of thalassemia, n			
β major	5	6	0.809
Severe HbE/β	18	18	
No available data	2	1	
Type of iron chelating agent, n			
Deferiprone	16	18	0.493
Deferasirox	8	6	
Deferasirox and desferrioxamine	1	0	
No iron chelating agent	0	1	
Current mean hemoglobin (SD), mg/dL	7.88 (1.16)	8.40 (0.85)	0.074
Previous mean hemoglobin (SD), mg/dL	7.88 (1.03)	8.15 (1.02)	0.347
AST level, n			
Increased	9	9	0.913
Normal	15	16	
No available data	1	0	
ALT level, n			
Increased	9	9	0.913
Normal	15	16	
No available data	1	0	
GFR, n (%)			
Glomerular hyperfiltration	20	16	0.133
Normal	4	9	
No available data	1	0	
Median ferritin (range), ng/mL	2,669 (229.58-9,756.69)	2,109 (437.85-7,001.91)	0.299
Mean duration of repeated transfusion (SD), years	8.32 (3.45)	5.49 (2.83)	0.003
Interval between transfusions, n			
< 4 weeks	18	12	0.087
> 4 weeks	7	13	
Mean vitamin D level (SD), ng/mL	20.00 (5.71)	20.46 (5.25)	0.765
Median IGF-1 level (range), ng/mL	91.43 (13.67-192.86)	161.3 (17.99-363.01)	0.011

Table 2. Multivariate analysis for variables associated with stunting in TDT children

Variables	B	Exp(B)	95%CI	P value
IGF-1 levels	-0.012	0.988	0.979 to 0.996	0.006
Sex (male)	-1.802	0.165	0.028 to 0.982	0.048
Duration of repeated transfusion	0.416	1.515	1.161-1.978	0.002

Multivariate analysis using multiple logistic regression (backward Wald method) showed that stunting in children with TDT had significant associations with low IGF-1 level, male sex, and longer duration of repeated transfusion (**Table 2**). Age, malnutrition, type of thalassemia, type of iron chelating agent, hemoglobin level, AST level, ALT level, GFR, ferritin level, and interval between transfusion were not associated by stunting in children with TDT.

Spearman's rank correlation analysis to investigate the relationship between vitamin D and IGF-1 levels in children with TDT revealed a correlation coefficient (r) of -0.473 ($P=0.001$). The correlation coefficient was -0.362 ($P=0.045$) in males ($n=31$ subjects) and -0.440 ($P=0.059$) in females ($n=19$ subjects). The associations between vitamin D and IGF-1 levels in males ($r=-0.218$; $P=0.257$) and females ($r=-0.337$; $P=0.186$) were no longer significant, after adjusting for age and nutritional status.

Discussion

Transfusion-dependent thalassemia has been known to have long-term complications, one of which is stunting. A cross-sectional study involving 367 children with transfusion-dependent β -thalassemia major in Pakistan showed that 65.4% of the total subjects had stunted growth (height-for-age Z-score < -2).¹⁷ Other recent study on growth pattern in children with TDT showed similar results with 65.71% of subjects suffering from stunting.¹⁸ The mechanism between TDT and stunting has been proposed to be due to altered IGF-1 regulation.

The IGF-1 mediates many physiological actions of growth hormone and is the major effector of bone growth. IGF-1 levels can be used as a predictor of height < -2 SD in adolescent patients with β -thalassemia major, with a cut-off point of < 38.51 ng/mL.¹⁴ Prior study showed that IGF-1 levels were lower in β -thalassemia major patients with impaired growth compared to those with normal growth, but this finding

was not statistically significant ($P=0.096$), possibly because of the small sample size of 19 and 14 children per group.¹⁹ We found that lower IGF-1 levels were associated with higher incidence of stunting. Further study is required to evaluate factors which mediate the association of IGF-1 and stunting in children with TDT and the molecular mechanism of IGF-1 modulation.

Children with TDT have a specific growth pattern that is relatively normal until the age of 9-10 years, after which, growth gradually slows.²⁰ Retardation in height growth occurs after the age of 11 years in boys and 9 years in girls.²¹ Height growth decreases with age, both in children who were initially stunted and children who were not stunted.¹⁷ We also noted that male sex was inversely related to stunting. Boys with TDT experienced height growth retardation at an older age than girls.

The longer TDT patients receive transfusions, the more likely they are to experience growth problems. Continuous transfusions can lead to accumulation of iron in the body organs, resulting in organ malfunction.²² Excessive iron interferes with maturation of osteoid and deposits in hydroxyapatite crystals, thus interfering with normal bone metabolism. Our results were consistent with this theory, in which stunted children had undergone longer duration of transfusions than the not stunted group.

In our study, vitamin D levels were not related to stunting in children with TDT. Vitamin D is a type 1 nutrient. If deficiency occurs, growth can still continue, but disrupted body function with specific clinical manifestations can lead to illness, disrupting growth in a secondary way.²³ Another possible explanation on the lack of association between vitamin D level and stunting may have been that nearly half subjects in both S and NS groups suffered from vitamin D insufficiency and deficiency (46%).

The relationship between vitamin D and IGF-1 remains unclear. It is well established that IGF-1 induces synthesis of $1,25(\text{OH})_2$ vitamin D in the kidney by stimulating 1α -hydroxylase and inhibits catabolism

by decreasing 24-hydroxylase gene expression.¹⁰ There is no conclusive mechanism by which vitamin D can modify IGF-1 and IGFBP-3 concentration. Cholecalciferol treatment for vitamin D deficient children can increase circulating IGF-1. Vitamin D supplementation can also increase serum IGFBP-3. The possible mechanisms by which vitamin D can increase IGF-1 and IGFBP-3 in circulation are by inducing liver synthesis through transcription of relevant genes and/or enhancement of GH stimulation, as well as by augmenting absorption of calcium in the intestine, since calcium intake is associated with circulating IGF-1.²⁴ A study in Lebanon examined the relationship between IGF-1 and vitamin D in 8 to 18-year-old children and found that IGF-1 levels in boys were inversely correlated with 25(OH) vitamin D. The correlation between IGF-1 and 25(OH) vitamin D was absent in both sex groups after adjusting for the main confounding variables (age, BMI, and height).²⁵ An explanation may be that the relationship between IGF-1 and 25(OH) vitamin D is not independent. Similarly, we found an inverse relationship between vitamin D and IGF-I levels in children with TDT. However, after controlling for the main confounding variables (age, sex, and nutritional status), the correlation did not retain significance, again suggesting that the relationship between vitamin D and IGF-I is not independent. Another possible explanation is that increased IGF-1 level induces changes from 25(OH) vitamin D to 1,25(OH)₂ vitamin D, thereby decreasing 25(OH) vitamin D levels. Further study needs to be conducted to explain this finding.

This study used the most recent results of liver function, renal function, and ferritin from patients' medical records, all of which were examined routinely every 3 months in our hospital. Such results might not accurately describe the conditions at the time of study onset. However, there was no significant correlation between liver function test and renal function test with stunting in TDT children in this study.

In conclusion, low IGF-1 levels are significantly associated with stunting in children with TDT. But we found no associations between vitamin D and stunting or between vitamin D and IGF-1 in children with TDT.

Conflict of interest

None declared.

Funding acknowledgment

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Vibrakasi V, Origa R. Genetic basis, pathophysiology and diagnosis. In: Cappellini MD, Cohen A, Porter J, Taher A, Vibrakasi V, editors. Guidelines for the management of transfusion dependent thalassemia (TDT). 3rd ed. Nicosia: Thalassaemia International Federation; 2014. p. 14-27.
2. Jahagirdar R, Parikh S, Deshpande R, Lalwani S. Growth profile of children with thalassemia major. IJAR. 2017;7:724-6.
3. Vogiatzi MG, Macklin EA, Trachtenberg FL, Fung EB, Cheung AM, Vichinsky E, et al. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. Br J Haematol. 2009;146:546-56. DOI: 10.1111/j.1365-2141.2009.07793.x.
4. Uda R, Idjradinata PS, Djais JTB. Risk factors to growth retardation in major thalassemia. MKB. 2011;43:21-5. DOI: 10.15395/mkb.v43n1.40.
5. Joseph N, Pai S, Sengupta S, Bharadwaj S, Dhawan S, Khare K. A clinico-epidemiological study of thalassemia cases in India. J Nat Sc Biol Med. 2018;9:236-41. DOI: 10.4103/jnsbm.JNSBM_224_17.
6. Fung EB, Aguilar C, Micaily I, Haines D, Lal A. Treatment of vitamin D deficiency in transfusion-dependent thalassemia. Am J Hematol. 2011;86:871-3. DOI: 10.1002/ajh.22117.
7. Shamshirsaz AA, Bekheirnia MR, Kamgar M, Pourzahedgilani N, Bouzari N, Habibzadeh M, et al. Metabolic and endocrinologic complications in beta-thalassemia major: a multicenter study in Tehran. BMC Endocr Disord. 2003;3:4. DOI: 10.1186/1472-6823-3-4.
8. Singh K, Kumar R, Shukla A, Phadke SR, Agarwal S. Status of 25-hydroxyvitamin D deficiency and effect of vitamin D receptor gene polymorphisms on bone mineral density in thalassemia patients of North India. Hematology. 2012;17:291-6. DOI: 10.1179/1607845412Y.0000000017.
9. Nakavachara P, Vibrakasi V. Children with hemoglobin E- α -thalassemia have a high risk of being vitamin D deficient even if they get abundant sun exposure: A study from Thailand. Pediatr Blood Cancer. 2013;60:1683-8. DOI: 10.1002/pbc.24614.
10. Singh SK. Study of growth promoting effect of vitamin D supplementation in vitamin D deficient hypothyroid children. Thyroid Res Pract. 2014;11:81-2. DOI: 10.4103/0973-

- 0354.129737.
11. Borgna-Pignatti C, Gamberini MR. Complications of thalassemia major and their treatment. *Expert Rev Hematol.* 2011;4:353-66. DOI: 10.1586/ehm.11.29.
 12. Hendarto A, Sjarif DR. Antropometri anak dan remaja. In: Sjarif DR, Lestari ED, Mexitalia M, Nasar SS, editors. Buku ajar nutrisi pediatrik dan penyakit metabolik jilid I. Jakarta: Badan Penerbit IDAI;2014. p. 25-37.
 13. Anggraeni AC. Antropometri. *Asuhan Gizi: Nutritional Care Process.* Yogyakarta: Graha Ilmu; 2012. p:1-33.
 14. Elizabeth M, Fadlyana E, Reniarti L, Faisal, Sukandar H, Rusmil K. Serum IGF-1 and short stature in adolescents with β -thalassemia major. *Paediatr Indones.* 2018;58:151-8. DOI: 10.14238/pi58.4.2018.151-8.
 15. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics.* 2008;122:398-417. DOI: 10.1542/peds.2007-1894.
 16. Cachat F, Combescure C, Cauderay M, Girardin E dan Chehade H. A systematic review of glomerular hyperfiltration assessment and definition in the medical literature. *Clin J Am Soc Nephrol.* 2015;10:1-8. DOI: 10.2215/CJN.03080314.
 17. Moiz B, Habib A, Sawani S, Raheem A, Hasan B, Gangwani M. Anthropometric measurements in children having transfusion-dependent beta thalassemia. *Hematology.* 2018;23:248-52. DOI: 10.1080/10245332.2017.1396044.
 18. Rathaur VK, Imran A, Pathania M. Growth pattern in thalassemic children and their correlation with serum ferritin. *J Family Med Prim Care.* 2020;9:1166-9. DOI: 10.4103/jfmpc.jfmpc_951_19.
 19. Ramadan M, Ebrahim NA, Ramadan MS, Salahedin O. Growth pattern in children with beta-thalassemia major and its relation with serum ferritin, IGF1 and IGFBP3. *J Clin Exp Invest.* 2012;3:157-63. DOI: 10.5799/ahinjs.01.2012.02.0135.
 20. Skordis N, Kyriakou A. The multifactorial origin of growth failure in thalassaemia. *Pediatr Endocrinol Rev.* 2011;8:271-7.
 21. Saxena A. Growth retardation in thalassemia major patients. *Int J Hum Genet.* 2003;3:237-46. DOI: 10.1080/09723757.2003.11885858
 22. Prabhu R, Prabhu V, Prabhu RS. Iron overload in beta thalassemia – a review. *J Biosci Tech.* 2009;1:20-31.
 23. Golden MHN. Specific deficiencies versus growth failure: type I and type II nutrients. *J Nutritional & Environmental Medicine.* 1996;6:301-8. DOI: 10.3109/13590849609007256.
 24. Ameri P, Giusti A, Boschetti M, Murialdo G, Minuto F, Ferone D. Interactions between vitamin D and IGF-I: from physiology to clinical practice. *Clinical Endocrinology.* 2013;79:457-63. DOI:10.1111/cen.12268.
 25. Gannagé-Yared MH, Chahine E, Farah V, Ibrahim T, Asmar N, Halaby G. Serum insulin-like growth factor I in Lebanese school children and its relation to vitamin D and ferritin levels. *Endocr Pract.* 2017;23:391-8. DOI: 10.4158/EP161623.OR.