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Original article

TNF-α and IGF-1 levels in stunting children with chronic infection

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Abstract. *Background and Objectives:* Stunting is a frequent nutritional issue among children worldwide. Stunted children have a high risk of having infection, which causes an increase in pro-inflammatory cytokines such as TNF-α and impairs linear growth rate in children, involving a decrease of IGF-1 hormone. The aim of this study is to analyze IGF-1 and TNF-α levels in stunting and non-stunting children with chronic infection. *Methods:* This was a cross-sectional study conducted at Husada Utama Hospital, Surabaya, Indonesia, from September 2023 to February 2024. Subjects were obtained using random sampling of a group of children aged ≤5 years with complaints of feeding difficulty, failure to gain weight, weight loss, and appearing short, including peers diagnosed to have chronic infection by professional medical staff. Subjects with fluid retention, organomegaly, tumor mass, congenital abnormalities, cerebral palsy, and hormonal disorders were excluded. Stunting was determined if the HAZ z-score was below -2 SD. *Results:* A total of 48 children, including 20 boys and 28 girls, were enrolled, and were divided into two groups: stunting (16 children) and non-stunting group (32 children). Stunting children were significantly younger than the non-stunting group. As expected, stunting children had significant lower body height and HAZ, and also significant lower body weight, WAZ and WHZ. TNF-a and IGF-1 levels were significantly lower in the stunting children group compared to the control group. There was a significant correlation between stunting and IGF-1 (OR: 0.915, 95% CI: 0.841 – 0.996). Cut-off value of IGF-1 to determine stunting was <4.43 (sensitivity 96.88%, specificity 43.75%). Cut-off value of TNF-α to determine stunting was >83.12 (sensitivity 90.63%. specificity 92.50%). *Conclusion:* TNF-a and IGF-1 levels were significantly lower in stunting children. IGF-1 was associated with a protective effect against stunting (OR 0.915). There was no correlation between stunting and TNF-a level.

Key words: stunting, chronic infections, TNF-a and IGF-1

Introduction

Stunting is a frequent nutritional issue among children worldwide (1). Based on 2018 data, approximately 149 million children, representing 21.9% of the total child population, were expected to suffer stunting (2). Asian countries were responsible for approximately 55% of the world's stunted children under the age of five. Indonesia has the third greatest prevalence of stunting in Southeast Asia, based on the World Health Organization (WHO) (3,4).

Stunted children under five years old were defined as having height-for-age z-score <–2 standard deviations based on World Health Organization (WHO) child growth standards (2,5). Stunted children also have high symptomatic and asymptomatic pathogen carriage (6,7), which results in a high risk of having infections leading to morbidity and mortality (8). In addition, malnutrition increases the risk of infection by lowering gut barrier function, affecting the intestinal microbiota, altering the regulation of inflammatory adipocytokines, and restricting the intake of critical micronutrients (9).

Meanwhile, the infection itself causes nutritional loss, decreased absorption, and elevated energy demands, leading to undernourishment (9). Infection also causes an increase in pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and impairs linear growth rate in children, which involves a decrease of insulin growth factor (IGF)-1 hormone (10–12). These excessive levels of TNF-α might induce anorexia and cachexia by increased blood leptin concentrations, which reduce appetite and results in impaired nutritional status (13,14). IGF-1 axis also plays an important role in regulating linear growth (15,16). IGF-1 primarily functions to provide the growth-enhancing actions of growth hormone (GH) in peripheral tissues (17). Thus, monitoring the IGF-1 serum levels might enhance the assessment of GH status in the examination of individuals with short stature and contribute in predicting the growth response (15,18).

Since stunting and chronic infection commonly occur together, we are interested in analyzing IGF-1 and TNF-α levels in stunting and non-stunting children with chronic infection.

Methods

Study design: This was a cross-sectional study conducted at the Nutrition and Metabolic Disease outpatient clinic of Husada Utama Hospital, Surabaya, Indonesia, from September 2023 to February 2024. In this study, we analyze TNF-α and IGF-1 levels in stunting and non-stunting children with chronic infection. Chronic infection in subjects were diagnosed by professional medical doctors (Figure 1).

Samples: Subjects were obtained using random sampling of children ≤5 years with complaints of feeding difficulty, lack of weight gain, weight loss, and appearing short, including peers diagnosed with tuberculosis by professional medical staff (TB score of 6 or more, a positive Mantoux test, chest x-ray suggestive of TB findings with supporting clinical symptoms and history of close contact with TB patient, urine culture with bacterial colonies $\geq 10^5$). Subjects with fluid retention, organomegaly, tumor mass, congenital abnormalities, cerebral palsy, and hormonal disorders, were excluded.

Measurements

Anthropometric measurements: Subject's body weight was measured using baby scale SECA 354 or standing scale SECA 813 (Hamburg, Germany) and recorded in grams. Subject's body height/length was measured using infantometer SECA 416 or stadiometer SECA 213 (Hamburg, Germany) and recorded in centimeters. The WAZ, HAZ and WHZ of each subject were calculated, based on the weight and height data, by using the WHO child growth standards. Stunting was determined if the HAZ z-score was below -2 SD.

Blood chemical measurements: Blood samples were taken and processed by professional local laboratory workers. 5 ml of blood was drawn from the vein for TNF-α and IGF-1 examinations. TNF-α was measured using the ELISA-Enzyme-linked

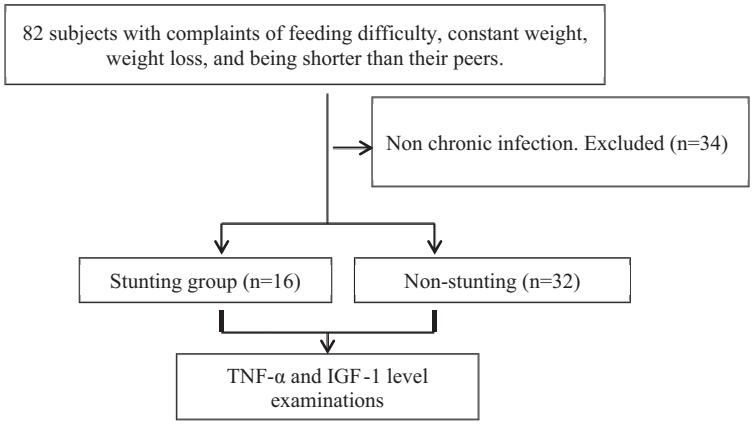

Figure 1. Study subject flow chart.

immunosorbent assay (E-EL-H0086; Elabscience, Inc., China). IGF-1 was measured using ELISA Kit (E 0082; Elabscience, Inc., China).

Statistical analysis

The statistical software tool SPSS version 24.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The presentation of descriptive statistics was based on the type of data. Testing for homogeneity of variation and normality was done on continuous data. Independent T-tests were performed if the distribution was normal or Mann-Whitney U-Test if the distribution was abnormal. Frequencies and percentages for categorical variables were compared utilizing the chi-square test. A binary logistic regression model was employed to examine the risk factors of IGF-1 and TNF-α levels that contribute to stunting, while receiver operating characteristic (ROC) curves were utilized to determine the cutoff values of IGF-1 and TNF-α for predicting stunting. A P value <0.05 indicated significant results (Figures 2, 3).

Results

A total of 48 children, including 20 boys and 28 girls, were enrolled in this study. These subjects were divided into two groups: stunting group which consisted of 16 children, and non-stunting group as the control group which consisted of 32 children. Subject's characteristics were summarized in Table 1.

There was no sex difference (P=0.679) between groups. Stunting children were significantly younger than the non-stunting group (11.30 + 1.99 vs. 8.27 + 1.53 kg, P<0.0001). As expected, stunting children

Table 1. Characteristics of patients.

Characteristics	Group (Mean +_SD)		p-value
	Stunting (n=16)	Non-stunting (n=32)	
Gender, n (%) • boys • girls	 6 (37.5%) 10 (62.5%)	 14 (43.8%) 18 (56.2%)	0.679[a]
Age, years old	1.50 +_0.44	2.26 +_0.91	0.006[d*]
Age (years) • <2 • 2 – <4 • 4 – 5	 10 (62.4%) 5 (31.3%) 1 (6.3%)	 19 (59.4%) 10 (31.3%) 3 (9.3%)	0.793[b]
Infection type • Urinary tract infection (UTI)+ Pulmonary TB • Pulmonary TB	 5 (31.3%) 11 (68.7%)	 11 (34.4%) 21 (65.6%)	0.829[a]
Exclusive breastfeeding for 6 months • yes • no	 15 (93.7%) 1 (6.3%)	 29 (90.6%) 3 (9.4%)	0.712[a]
Body weight, kg	8.27 + 1.53	11.30 + 1.99	<0.001[d*]
Body height. cm	74.25 + 5.94	86.20 + 8.48	<0.001[d*]
WAZ, z-score	-2.21 + 1.17	-0.86 + 0.83	<0.001[d*]
HAZ, z-score	-2.86 + 0.67	-0.88 + 0.71	<0.001[d*]
WHZ, z-score	-1.29 + 0.96	-0.59 + 1.08	0.032[d*]
TNF-α, pg/ml	134.567 ± 136.285	173.723 ± 98.842	0.037[c*]
IGF-1, ng/ml	8.409 ± 11.074	14.994 ± 9.515	0.007[c*]

[a]Chi-square test; [b]Kruskall Wallis test; [c]Mann-Whitney U test, [d]Independent T test; Mean ± SD; SD = Standard Deviation. *P<0.05 = statistically significant

Abbreviation: UTI = urinary tract infection; TB = tuberculosis; WAZ = weight-for-age z-score; HAZ = height-for-age z-score; WHZ = weigh-for-height z-score; TNF-α = tumor necrosis factor-α; IGF-1 = insulin-like growth factor-1

Table 2. Logistic Regression in IGF-1 and TNF-α level with stunting.

Variable	p-value	OR	95% CI Lower - Upper
IGF-1 (ng/ml)	0.040*	0.915	0.841–0.996
TNF-α (pg/L)	0.171	0.995	0.988–1.002

OR = Odds Ratio; CI = Confidence Interval; *P<0.05 = statistically significant.

group had significant shorter body height (11.30 + 1.99 vs. 8.27 + 1.53 kg, P<0.0001), and lower HAZ score (-2.86 + 0.67 vs. -0.88 + 0.71, P<0.0001) than the control group.

Stunting children also showed significant lower body weight (8.27 + 1.53 vs. 11.30 + 1.99 kg, P<0.0001), WAZ (-2.21 + 1.17 vs. -0.86 + 0.83, P<0.001), and WHZ (-1.29 + 0.96 vs. -0.59 + 1.08, P<0.0001). TNF-α serum levels (134.567 ± 136.285 vs. 173.723 ± 98.842 pg/ml, P=0.037) and IGF-1 levels (8.409 ± 11.074 vs. 14.994 ± 9.515 ng/ml P=0.007), were significantly lower in the stunting children group compared to the control group.

There was a significant correlation between stunting and IGF-1 which showed that a one-unit increase in IGF-1 correlates with a 9.15% reduction in the risk of stunting (95% CI: 0.841 – 0.996, P=0.40). Meanwhile, we found no significant correlation between stunting and TNF-α (Table 2).

The area under the curve (AUC) of IGF-1 in predicting the existence of stunting was 0.717 (95% CI: 0.548– 0.885). Cut-off value of IGF-1 to determine stunting was <4.43 (sensitivity of 96.88% and specificity 43.75%, P=0.015).

The AUC of TNF-α in predict stunting was 0.686 (95% CI: 0.485– 0.886). Cut-off value of TNF-α to determine stunting was >83.12 (sensitivity 90.63% and specificity 92.50%, P=0.038).

Discussion

Over half of 82 initial prospective subjects who had complaints of feeding difficulty, failure to gain weight, weight loss, and being shorter than their peers, were found to have chronic infection, and 33.33% of them were already suffering from stunting. These results support our hypotheses above, that the presence of infection is associated with decreased appetite, resulting in reduced nutrient intake, which leads to an impaired trajectory of child growth. Others have noted that appetite pathway was disrupted during infection and inflammation (19). Leptin, frequently referred as the satiety factor, suppressed body weight by reducing appetite and enhancing expenditure of energy (13). Other hormones that also reduce the appetite are OXM, GLP-1 and GLP-2 (20). In addition, there is a twofold nutritional stress associated with infections. First, anorexia causes a decrease in food intake. Second, there is an increase in demand for amino acids, which are needed for faster acute phase protein synthesis, glutathione formation, and the development of an adaptive immunological response. All of these nutritional stresses lead to undernutrition (21).

In this study, we also discovered that children in the stunting group were significant younger than the non-stunting group. Furthermore, we classified individuals into age groups (<2 years, 2-4 years, >4 years) in order to determine the highest prevalence of stunting. Our findings indicate that children under the age of 2 years had a higher prevalence of stunting compared to other age groups; however, this difference was not statistically significant. A prior study found that certain children who were previously classified as stunted before the age of 2 may recover to a non-stunted state after the age of 2 (22). Another study also explained that there is a catch-up growth potential even if the child is already older than 2 years (21).

In accordance with our hypotheses above, we found that stunting was associated with significantly lower IGF-1 levels; IGF-1 had a protective effect against stunting (OR 0.915). Our finding is supported by several studies, including a study in Bangladesh of children aged between 12 and 18 years without acute or chronic infection (IGF-1 58.34.6 vs. 51.6 + 35.1 pg/ml) (23); also a study in Indonesia which included prepubertal stunted children with transfusion-dependent thalassemia (91.43 vs. 161.3 pg/ml)(24). In our study, the mean level of IGF-1 in stunted children was lower than those studies. This suggests that children with stunted and chronic infection may have lower IGF-1

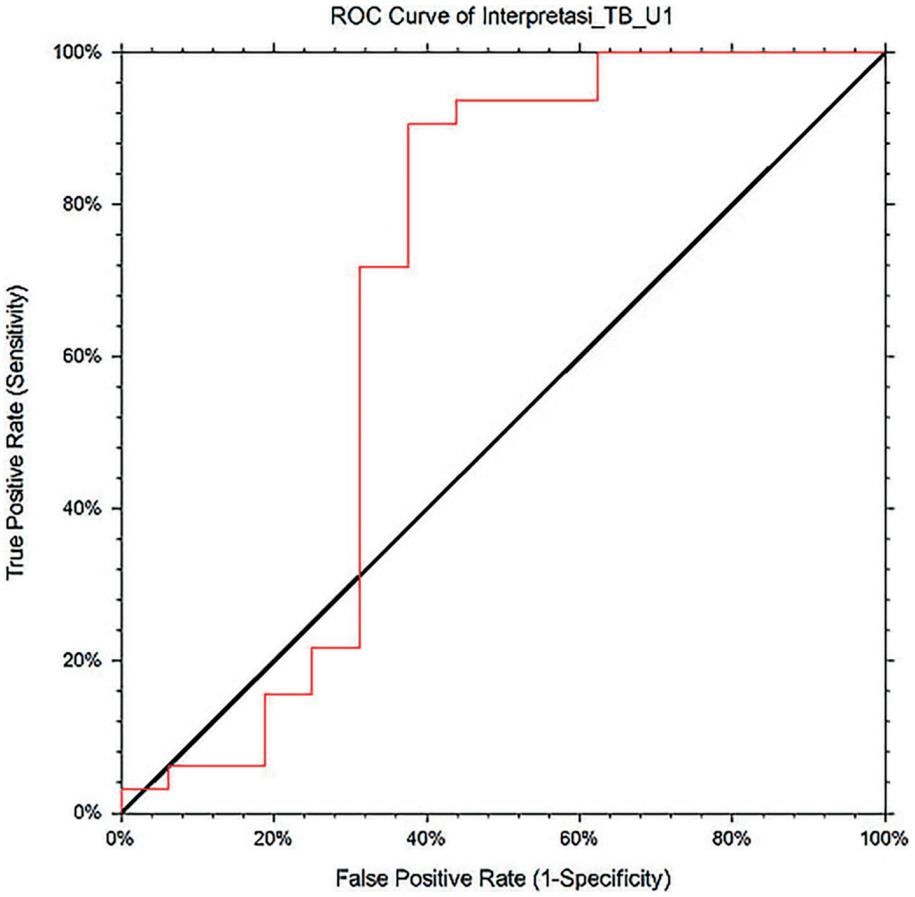

Figure 2. Receiving operation curve (ROC) of IGF-1 level to detect stunting in children with chronic infection.

levels than stunted children with several conditions without infection. These lower IGF-1 levels in stunted children can be explained by the prolonged dietary restriction with reduced caloric intake, which in turn lead to reduced fat mass and falling insulin concentrations, and to restricted leptin production (25). These low levels of leptin may stimulate the hypothalamic-pituitary axis and possibly the axis of hypothalamic-pituitary-GH, to maintain the elevated cortisol and GH levels required for efficient lipolysis as a fuel supply (fatty acids) for brain and peripheral tissue metabolism during nutritional deprivation. This mechanism may cause IGF-1 synthesis reduction, altering the growth hormone axis in childhood (11,26). Meanwhile, the IGF-1 also might play a protective role for the host from deadly bacterial infections by promoting myeloid cell maturation, stimulating phagocyte migration, encouraging phagocytes to produce superoxide anions and cytokines, and increasing opsonic activity. Therefore, lower IGF-1 levels might interfere with immune regulatory functions during malnutrition which increases risk of infection (27). This study used IGF-1 as a growth biomarker in stunting because it is more sensitive to nutritional deficiencies than other biomarkers such as IGF binding protein-3 (28), and also is more stable than growth hormone (GH) and not affected by diurnal fluctuations and pre-analysis factors such as food intake, exercise, and stress before blood sampling (29). We found that the cut-off value of IGF-1 was <4.43 (sensitivity of 96.88%, specificity 43.75%); these results were also lower than the study in Indonesia which showed ≤ 38.51 ng/ml (24).

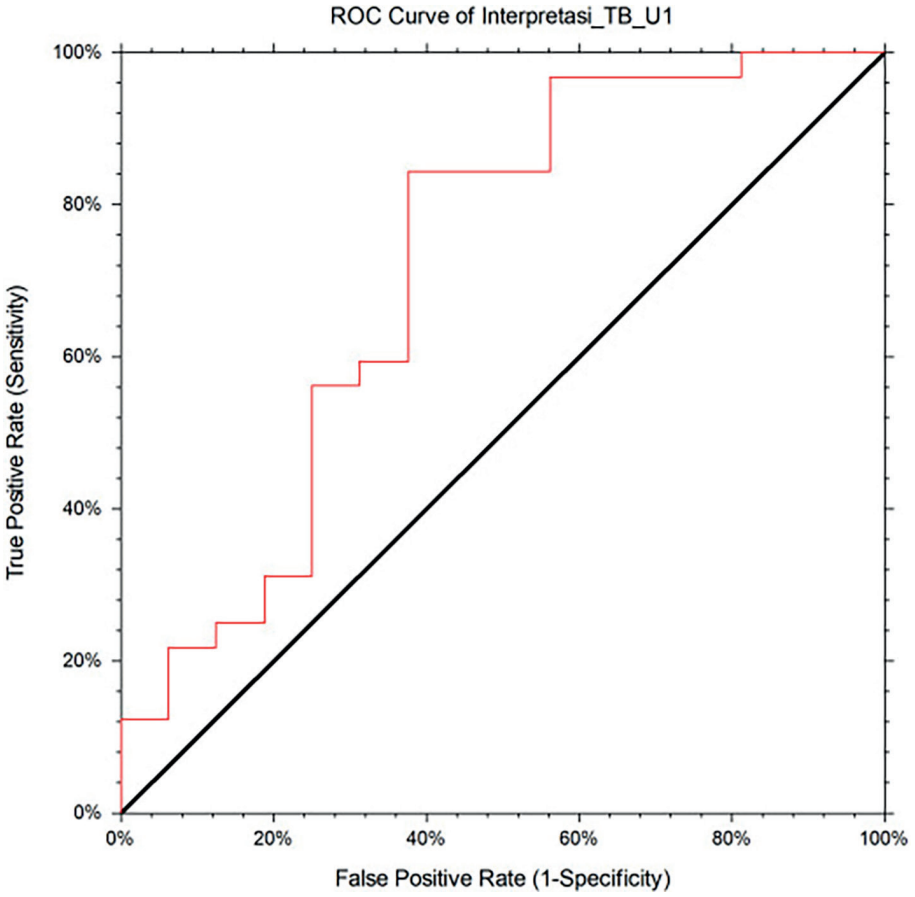

Figure 3. Receiving operation curve (ROC) of TNF-α level to detect stunting in children with chronic infection.

In addition, our results using bivariate analysis on TNF-α levels showed a significant difference between stunted and non-stunted children. Our analysis contradicts the hypothesis we presented above which postulated that TNF-α was higher in stunted children with chronic infection. The possible reason is that the immunological responses in stunted children are altered. The synthesis of pro-inflammatory cytokines, such as TNF-α, by bone marrow cells is reduced as a result of chronic malnutrition (23,30). Also, undernutrition compromises the body's immune system, making it more susceptible to infections. So the body responds by suppressing cellular immunity as a strategic approach to avoid autoimmune responses (23,31). Prior studies had reported that some pro-inflammatory cytokines such as IL-6, TNF-α, IL-1, and IFN-γ levels in children with undernutrition (23, 32–34), were lower in stunting children with chronic infection, which supports our results. A study by Hossain (23) reported that blood leptin production was decreased, while TNF-α level in was also low in stunted children with chronic infection. In addition, we also discovered the cut-off value of TNF-α to determine stunting was >83.12 pg/ml. According to our knowledge, this finding was the first to set the cut-off for TNF-α level to determine stunting.

Infectious diseases are likely to be the cause of stunting, coexisting with poor diet, which is recently a major public health concern. Infections might worsen malnutrition, as appetite is suppressed and food intake is reduced, and any malabsorption reduces nutrient intake, while malnutrition lowers the immune system

and exacerbates the effects of infection (35). Chronic infections that we found in this study were pulmonary tuberculosis (TB) and pulmonary TB infection accompanied by UTI. TB is already reported closely related to the nutritional status of children. Meanwhile, children who experience malnutrition also had a higher risk of suffering from TB (36). A study conducted in Jakarta, Indonesia reported that malnourished children dominated in a group with TB infection (37) Another study conducted in Surabaya, Indonesia also stated that children with poor nutritional status were two times more likely to contact infections such as TB (38,39).

This study's strengths were the focus on the specific population of children with chronic infection which contribute significant regional data to the worldwide literature on stunting; the strategic use of IGF-1 and TNF-α as markers is reasonable, provided both have been associated with the mechanisms underlying stunting; and the utilizing ROC curves to determine cutoff values enhances the findings' complexity.

Meanwhile, this study also had several limitations. First, the current study used a cross-sectional design, which only provides data overview at one point in time. Therefore, this study design could not imply causality in risk factors affecting TNF-α and IGF-1 levels. Second, data collection in this study was carried out on one occasion without a follow-up period, which might create bias in observations because it could not take into account seasonal variations or changes in children's lifestyles over time. Observations conducted over a longer period of time might provide more representative results. Finally, this study was a single-center study, and the sample size was small. This study was also conducted in a private hospital, and it was difficult to include chronic infection patients without other comorbid diseases.

Conclusion

In children with chronic infection, TNF-a and IGF-1 levels were significantly lower in stunting children compared to non-stunting. IGF-1 was associated with a protective effect against stunting (OR 0.915). There was no correlation between stunting and TNF-a level.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Author Contributions: S.N: Data curation, data analysis, recruitment, drafting; N.A.W: Supervising, drafting, methodology, data curation, fundings; D.H: Supervising, editing, revision. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Declaration on the Use of AI: None.

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