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Cut off Point of Insulin-Like Growth Factor-I (IGF-1) for Prediction of Child Stunting

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Abstract

Objectives: The aim of this study was to determine cut off point of Insulin-Like Growth Factor-I (IGF-1) for prediction of child stunting.

Method: This prognostic model was conducted subdistrict of Pasaman and West Pasaman, West Sumatera, Indonesia from July-November 2018. This study was performed on 185 children aged 0-3 years, consist of stunting group 94 respondents and not stunting 91 respondents. Determination of insulin-like growth factor-I (IGF-I) expression levels using the qRT-PCR method. Total RNA from blood samples of stunting and normal children was extracted using Trizol and stunting assesment using z-score index Height per age where the result ≤-2 SD is stunting. The mean difference of IGF-I level was analyzed by independent sample T test. A two-tailed *P*-value of <0.05 was considered statistically significant. Cut off point analysis using receiver operating characteristic (ROC) curve, the results show sensitivity, specificity and an accuracy. Data were analyzed using the SPSS version 20.0

Results: The results showed IGF level in child stunting 10.44±9.88 ng/ml and 10.09±10.08 ng/ml in child not stunting. Cut off point IGF-I for prediction of child stunting is 6.63 ng/ml with 64.2% sensitivity, 60.0% specificity and accuracy 61,3%.

Conclusion: This analysis confirmed IGF-I can predict child stunting with enough accuracy for classification.

Keywords: *Child, classification, IGF-1, prediction, stunting.*

Introduction

Stunting is the best summary measure of chronic malnutrition in children. Approximately one-quarter of children under age 5 worldwide are stunted. Stunting is an intractable public health problem affecting around one-third of children in developing countries.[1] Stunting underlies 14–17% of child deaths globally and causes long-term cognitive defects, fewer years and poorer performance at school, lower adult economic productivity and an increased risk of stunting into subsequent generations.[1,2] Poor linear growth begins *in utero*, continues during the first 2 years of life and is largely irreversible thereafter.[3] Despite its high prevalence, the reasons for stunting among children living in impoverished conditions remain uncertain. Although inadequate diet contributes to poor growth, the best nutritional interventions have only a modest impact on stunting.[4] Diarrhea has been implicated in the causal pathway to stunting but, possibly because children frequently show catch-up growth between diarrheal episodes,[5] the association has been surprisingly weak in many studies. The role of the gut in mediating stunting

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has been relatively overlooked until recently, when attention has refocused on the possible contribution of enteropathy to poor growth in early life.[6,7]

Stunting affects one-third of children in developing countries, but the causes remain unclear. Stunting began *in utero* and was associated with low maternal IGF-1 levels at birth. Inflammatory markers were higher in cases than controls from 6 weeks of age and were associated with lower levels of IGF-1 throughout infancy.[1]

Stunting may therefore be driven by intestinal damage and chronic inflammation in addition to dietary inadequacy. Furthermore, since stunting begins *in utero*, the maternal inflammatory environment may have an important influence on fetal growth. However, few longitudinal studies have evaluated the mechanisms underlying poor growth among infants in developing countries. We hypothesized that an important cause of child stunting is exposure to chronic, low-grade inflammation during fetal and postnatal life, which suppresses production of IGF-1 perturbing the growth hormone axis early in life. We hypothesized that enteropathy leads to low-grade inflammation, which suppresses the growth hormone-IGF axis and mediates stunting.[8,9]

Method

Study design and research sample: This prognostic model was conducted subdistrict of Pasaman and West Pasaman, West Sumatera, Indonesia from July-November 2018. This study was performed on 185 children aged 0-3 years, consist of stunting group 94 respondents and not stunting 91 respondents. The sample size was calculated using the formula for continuous data on population.

Operational definitions: The variables of this study divided into independent variables, that is IGF-1; and a dependent variable, that is stunting.

Ethics statement: The study was approved by the ethical committee board of Faculty of Medicine Universitas Andalas, Padang City, Indonesia Number 495/KEP/FK/2017. Written informed consent was obtained from all respondents.

Data collection technique: Determination of IGF-I expression levels using the qRT-PCR method. Total RNA from blood samples of stunting and normal children was extracted using Trizol and stunting assesment using z-score index Height per age where the result ≤-2 SD is stunting.

Data analysis: The quantitative variables were recorded as Mean±SD, median and percentage. The mean difference of IGF-I level was analyzed by independent sample T test. A two-tailed *P*-value of <0.05 was considered statistically significant. Cut off point analysis using receiver operating characteristic (ROC) curve, the results show sensitivity, specificity and an accuracy. Data were analyzed using the SPSS version 24.0.

Results

Data characteristics of the respondents (Table 1).

Table 1: Characteristics of the respondents

Variables	Nutrition Status		p value
	Stunting (n=94)	Not Stunting (n=91)	
Child Characteristics			
Child's age (months), mean±SD	23.97±6.74	24.44±6.95	0.640
Birth weight (gram), mean±SD	3284.04±480.65	3210.88±478.83	0.301
Family Characteristics			
Family head's education, f(%)			
Low	62 (65.9)	42 (46.1)	0.003*
Moderate	13 (13.9)	18 (19.8)	
High	19 (20.2)	31 (34.1)	
Salary per months (Rp), mean±SD	717375±144713	1417349±202534	0.081
Family member, mean±SD	4.78±1.61	5.07±1.73	0.240

Table 1 known there were statistically significant mean difference child's age, birth weight, salary per months of head family and familiy member between stunting and not stunting groups (p>0.05). There was statistically association family head's education between stunting and not stunting groups (p<0.05).

Mean difference of IGF-I levels between child stunting and not stunting (Table 2).

Table 2: Mean difference of IGF-I levels between child stunting and not stunting

Variable	Mean±SD	p value
Child stunting (ng/ml)	10.44±9.88	0.047
Not stunting (ng/ml)	10.09±10.08	

Table 2 showed IGF-I level in child stunting 10.44±9.88 ng/ml and 10.09±10.08 ng/ml in child not stunting. There was statistically significant mean difference IGF-1 levels with stunting (p<0.05).

Determination of the cut off point of IGF-I level (Figure 1).

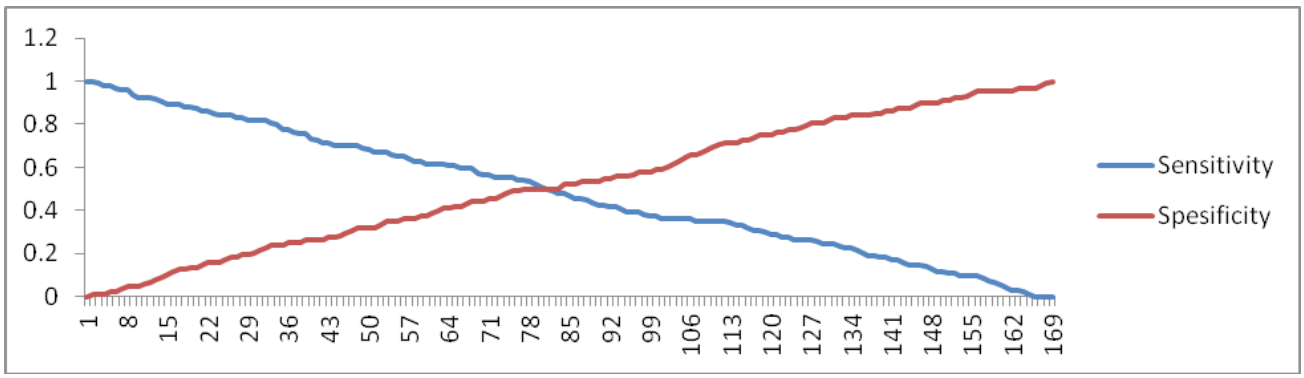

Figure 1: Determination cut off point of IGF-I for prediction of child stunting

Figure 1 showed cut off point of mechanistic target of rapamycin complex 1 (mTORC1) for prediction of child stunting in cut off point 77. The cut off point from the optimal cut off point of lines and the acquisition of sensitivity and specificity (Table 3).

Table 3: Cut off point IGF-I from the optimal cut off point of lines and the acquisition of sensitivity and specificity

No	Cut off point	Sensitivity	1 - Specificity	Sensitivity	Spesificity
1	-1	1	1	1	0
2	0.214	1	0.988636364	1	0.011364
3	0.49	0.989362	0.988636364	0.989361702	0.011364
4	0.562	0.978723	0.988636364	0.978723404	0.011364
5	0.593	0.978723	0.977272727	0.978723404	0.022727
6	0.645	0.968085	0.977272727	0.968085106	0.022727
7	0.707	0.957447	0.965909091	0.957446809	0.034091
8	0.748	0.957447	0.954545455	0.957446809	0.045455
9	0.7685	0.93617	0.954545455	0.936170213	0.045455
10	0.7895	0.925532	0.954545455	0.925531915	0.045455
11	0.81	0.925532	0.943181818	0.925531915	0.056818
12	0.841	0.925532	0.931818182	0.925531915	0.068182

13	0.8825	0.914894	0.920454545	0.914893617	0.079545
14	0.9135	0.904255	0.909090909	0.904255319	0.090909
15	0.9345	0.893617	0.897727273	0.893617021	0.102273
16	0.976	0.893617	0.886363636	0.893617021	0.113636
17	1.0275	0.893617	0.875	0.893617021	0.125
18	1.0585	0.882979	0.875	0.882978723	0.125
19	1.0895	0.882979	0.863636364	0.882978723	0.136364
20	1.1305	0.87234	0.863636364	0.872340426	0.136364
21	1.1615	0.861702	0.852272727	0.861702128	0.147727
22	1.1825	0.861702	0.840909091	0.861702128	0.159091
...					
77	6.63	0.542553	0.5	0.642553191	0.6
78	6.6815	0.531915	0.5	0.531914894	0.5
79	6.7025	0.521277	0.5	0.521276596	0.5
80	6.723	0.510638	0.5	0.510638298	0.5
...					
167	37.4665	0	0.022727273	0	0.977273
168	45.3645	0	0.011363636	0	0.988636
169	53.673	0	0	0	1

Table 2 showed based on analysis, we obtained cut off point IGF-I for prediction of child stunting is 6.63 ng/ml with 64.2% sensitivity and 60.0% specificity. Accuracy for cut off point of IGF-I showed in Receiver Operating Characteristics (ROC) (Figure 2).

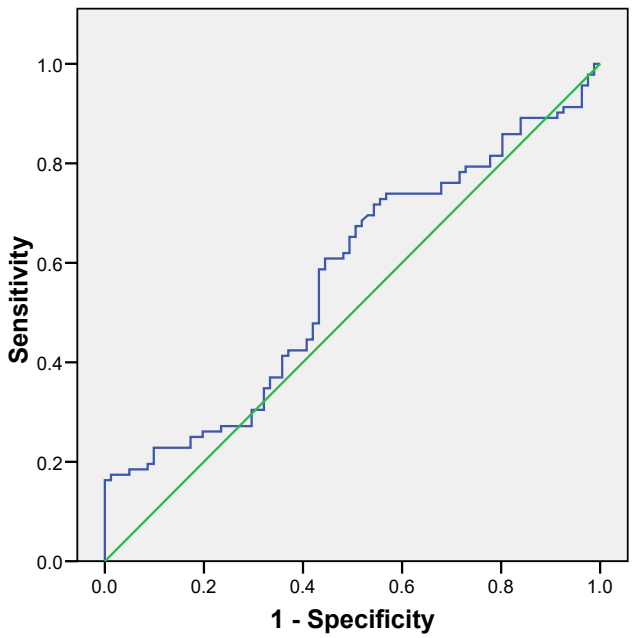

Figure 2: Receiver Operating Characteristics (ROC) for known accuracy of cut off point of IGF-I for prediction of child stunting

Figure 2 showed accuracy of IGF-I cut off point is 61.3%, it is means poor clasification.

Discussion

The results showed IGF level in child stunting 10.44±9.88 ng/ml and 10.09±10.08 ng/ml in child not stunting. Cut off point IGF-I for prediction of child stunting is 6.63 ng/ml with 64.2% sensitivity, 60.0% specificity and accuracy 61,3%..

Levels of IGF-1 were generally low compared to reported values from European infant cohorts.[10,11] However, levels of IGF-1 and its principal binding protein IGFBP3 were consistently lower among stunted compared to non-stunted infants from as early as 6 weeks of age. Whether reduced IGF-1 levels are a cause or a consequence of stunting is difficult to ascertain from our data, but given the well-characterized function of IGF-1 at growth plates, we speculate that lower levels are likely to mediate stunting in early life. In chronic inflammatory diseases such as juvenile idiopathic arthritis and Crohn's disease, elevated proinflammatory cytokines mediate growth failure through a reduction in circulating IGF-1.[8,9] Similarly, in our cohort of apparently healthy Zimbabwean infants, elevated inflammatory markers (even within the clinically normal range) were associated

with reduced IGF-1 levels. The association between low-grade chronic inflammation and suppression of the growth hormone-IGF axis was apparent soon after delivery and may account for the decline in linear growth that occurs from birth among African and Asian infants.[3] IGF-1 levels remained lower in stunted infants throughout the first year of life, but by 18 months levels were similar between groups. This suggests that a window of opportunity may exist in infancy, during which interventions to reduce inflammation and increase IGF-1 may improve linear growth.

Birth weight was related to infant IGF-1 at birth, which in turn was associated with the inflammatory status of the mother-infant dyad. The infant inflammatory milieu was closely related to the level of maternal inflammation at birth. We speculate, based on these associations, that inflammation during pregnancy may 'set' the infant inflammatory axis, which in turn influences the level of IGF-1 in early life. Optimizing the health of pregnant women may be essential to impact antenatal and postnatal stunting. Infants who became stunted were born to mothers who themselves were shorter than mothers of non-stunted infants. However, it was striking that over one-quarter of mothers of cases were overweight or obese. The relationship between maternal and fetal nutritional status is therefore complex and requires further investigation, particularly in view of the emerging obesity epidemic in countries that are experiencing the nutrition transition.[12,13,14]

In summary, our data suggest that stunting is influenced by both maternal and infant factors. Antenatally, maternal nutritional and inflammatory status may impact fetal growth, leading to intrauterine stunting and low birth weight; postnatally, low-grade inflammation early in life is associated with stunting.

Conclusion

This analysis confirmed IGF-I can predict child stunting with enough accuracy for classification.

Conflict of Interest Statement: The authors declared no potential conflicts of interest

Funding: Not applicable

Ethical Clearance: The study was approved by the ethical committee board of Faculty of Medicine Universitas Andalas, Padang City, Indonesia Number 495/KEP/FK/2017. Written informed consent was obtained from all respondents.

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