Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Jul 16; 10(B):1-6.
https://doi.org/10.3889/oamjms.2022.9551
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Pediatrics*

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The Higher C-Reactive Protein Levels as a Risk Factor of Stunting in Children with Acyanotic Congenital Heart Disease

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Edited by: https://publons.com/researcher/391987/mirko-spiroski/
Citation: Pangestika NPW, Putra IGNS, Sidiartha IGL, Windiani IGAT, Gunawijaya E, Mahalini DS, Sukmawati M. The Higher C-Reactive Protein Levels as a Risk Factor of Stunting in Children with Acyanotic Congenital Heart Disease. Open Access Maced J Med Sci. 2022 Jul 16; 10(B):1-6. https://doi.org/10.3889/oamjms.2022.9551
Keywords: C-reactive protein; Congenital heart disease; Stunting
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Received: 26-Mar-2022
Revised: 26-Apr-2022
Accepted: 06-Jul-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Children with acyanotic congenital heart disease (CHD) had a high risk of stunting. In addition to inadequate nutrition, chronic inflammatory process also plays an important role. An increase in serum c-reactive protein (CRP) suppresses insulin like growth factor 1 (IGF-1) production, causing disorder in child growth.

AIM: The objective f the study was to prove that higher CRP levels as a risk factor of stunting in children with acyanotic CHD aged 6–24 months old.

METHODS: This study is an observational analytic study with a case–control design, to assess higher CRP levels as a risk factor of stunting in children with acyanotic CHD aged 6–24 months old. This research was conducted at the Pediatric Cardiology Polyclinic, Sanglah Hospital from May to December 2021 with the consecutive sampling method. Data analysis was performed using the Chi-square test or Fisher's absolute test. Multivariate analysis with binary logistic regression was performed on all variables. Significance level was $p < 0.05$.

RESULTS: This study involved 60 subjects, consisting of 30 subjects with stunting and 30 subjects with no stunting. Children with stunting had higher mean CRP levels, 2.4 (±3.7) and 1.2 (±0.6). CRP level ≥3 mg/dL ($p = 0.031$; aOR 22.89; 95% CI 1.32–395.39) was a risk factor of stunting in children with acyanotic CHD. Other risk factors that significant are male, living in rural areas, low birth weight, and under-nutrition.

CONCLUSION: Higher CRP levels as a risk factor of stunting in children with acyanotic CHD. Other significant risk factors include males, living in rural areas, low birth weight, and under-nutrition.

Introduction

Congenital heart disease (CHD) is the most common structural malformation in children, occurring in 0.5–0.8% of all births [1]. Children with CHD often face growth disorders, including stunting. Stunting is a major public health problem. Stunting causes irreversible physical and mental damage to children, especially in the first 1000 days of a child's life. Several major factors contribute to the catch-up growth of children with CHD, including increased caloric requirements and body metabolism, decreased intake (anorexia) due to difficulty to eat and drink (intermittent eating and drinking), impaired utilization, absorption of nutrition, and presence of recurrent infections [2], [3].

Acyanotic CHD can result in hemodynamic disturbances, such as volume overload or pressure on the heart. Hemodynamic abnormalities led to activation of inflammatory cytokines that resulted in damage of cardiac myocytes, formation of fibroblasts, and vascular endothelial cell dysfunction. This condition results in pathological conditions such as cardiac hypertrophy, fibrosis, and damage to heart cells, thereby reducing heart function [4], [5], [6]. The c-reactive protein is a simple inflammatory marker that can be elevated in conditions such as congenital heart disease and stunting. This marker is easy to perform, available in every health service, and has good sensitivity and specificity. The c-reactive protein has a sensitivity of 65% and specificity of 85% to assess inflammation [7]. Pathological conditions in the heart can be characterized by increased levels of CRP in the blood. The 2015 Jones criteria used a CRP level cut-off of 3 mg/dL to assess the inflammatory process of the heart in children with rheumatoid arthritis. The c-reactive protein levels are used to indicate the functional status of the heart muscle and cardiac vascular abnormalities in children. An increased CRP levels suppresses IGF-1 production, causing disorder of child growth or stunting [5], [6].

Although previous studies have suggested an association between CRP and stunting in children with acyanotic CHD [8], [9], there is still controversy regarding the association between stunting and inflammation, with some clinical studies showing no anti-inflammatory effects. Ahasmi *et al*. reported CRP levels are not associated with stunting in children aged 2–5 years old [10]. These conflicting results make the evidence should be cautiously applied in the general population. The absence of data or similar research conducted in Indonesia warrants further investigation about higher CRP levels as a risk factor of stunting in children with acyanotic CHD at different geographical.

Materials and Methods

Study design and population

This study is a case–control study that is conducted from May to December 2021. It was performed in the pediatric cardiology clinic of Sanglah Hospital, as a tertiary health facility in Denpasar, Bali, Indonesia. Children with acyanotic CHD aged 6–24 months with or without stunting were included in this study. Those children who were suffering complications as heart failure, familial short stature, immune system disease/immunocompromised, endocrine/hormonal diseases, chronic disease, infection disease, malignancy, genetic/chromosomal disorders, musculoskeletal disorders, long-term steroid use, or the parents/guardians were not willing to participate in the study, were excluded from the study. The sample size was determined by different proportions, two independent group's formula. Based on this calculation, the sample size in this study was 30 subjects in each group, so the total required subjects were 60 children. All eligible children who were treated at Sanglah Hospital were included as study subjects consecutively.

Data collections

Complete information about this research will be provided to each parent to then ask for the willingness to cooperate in this research, as well as sign a research approval letter. After signing informed consent, the parent was interviewed to collect basic characteristics such as place of birth, age, gender, and address. At the time of the interview, the body weight and height of the subject were measured accordingly. Blood samples were taken from each patient for CRP evaluation.

Acyanotic CHD was determined based on clinical symptoms and echocardiography results. Chronic nutritional status was determined by taking anthropometric measurements of body length. The measurement results will then be plotted into a table based on length-for-age according to the anthropometric standard in the Regulation of The Minister of Health of The Republic of Indonesia 2020. Children are defined as stunting if their length for age is below two standard deviations and non-stunting if length for age is above two standard deviations. The c-reactive protein level is an acute-phase protein determined by laboratory checking with the Alinity C apparatus and the immunoturbidimetric method. The c-reactive protein levels were determined to be high if the results were more than 3 mg/dL.

Statistical analysis

Analysis was performed by SPSS for windows version 23.0. Characteristic data were expressed using mean (standard deviation) or median (interquartile range) for normal-distributed or not normal-distributed continuous variables, and in frequency and percentage for categorical variables. The hypothesis test for different proportions of two independent groups used the Chi-square test or Fisher's absolute test to calculate the Odds Ratio (RO). Multivariate analysis using binary logistic regression was performed on all variables in this study. The significance level (α) of this study was set at a probability value (p) of <0.05. This study was approved by Research Ethics Committee at Faculty of Medicine Udayana University/Sanglah Hospital, Denpasar (956/UN14.2.2.VII.14/LT/2021) and the Indonesian Ministry of Health, Directorate General of Health Services Sanglah Hospital (LB.02.01/XIV.2.2.1/1823/2021)

Results

This research was conducted at the pediatric cardiology polyclinic of Sanglah Hospital from May to December 2021. The total sample of the study was 60 subjects, consisting of 30 subjects with stunting and 30 subjects without stunting. The characteristics of subjects with stunting were 63.3% children aged >12 months with a mean age of 15.8 ± 6.4 months, most subjects were male (66.7%), lived in rural areas (73.3%), gestational age ≥37 weeks (90.0%), education level of fathers and mothers are high (60.0% and 63.3%), and the number of siblings is ≤2 children (90.0%). In this study, children with stunting had a higher mean CRP level than children without stunting, with a mean of 2.4 (±3.7) and 1.2 (±0.6). The characteristics of the subjects are shown in Table 1.

The c-reactive protein levels were analyzed using Fisher's exact test and presented with a large effect odds ratio (OR) with a 95% confidence interval (CI). Multivariate analysis with binary logistic regression was performed on all variables. The c-reactive protein levels ≥3 mg/dL (p = 0.031; aOR 22.89; 95% CI 1.32–395.39) as a risk factor of stunting in children with acyanotic CHD. Other significant factors were gender (p = 0.006; aOR 10.85; 95% CI 1.95–60.37), living in rural areas (p = 0.014; aOR 13.51; 95% CI 1.71–106.77), birth weight ≤2500 g (p = 0.004; aOR 61.36; 95% CI 3.72–1009.91), and under-nutrition (p = 0.004; aOR 27.45; 95% CI 3,11–241.77). The results of the analysis are shown in Table 2.

Table 1: Characteristic of subjects

Characteristic	Stunting (n = 30)	Control (n = 30)	Total (n = 60)
Age (months), mean (± SD)	17.6 (± 5.8)	14.1 (± 6.5)	15.8 (± 6.4)
≤ 12 months	8 (26.7)	14 (46.7)	22 (36.7)
> 12 months	22 (73.3)	16 (53,3)	38 (63.3)
Gender, n (%)			
Male	20 (66.7)	8 (26.7)	28 (46.7)
Female	10 (33.3)	22 (73.3)	32 (53.3)
Residence, n (%)			
Rural	22 (73.3)	20 (66.7)	42 (70.0)
Urban	8 (26.7)	10 (33.3)	18 (30.0)
Gestational age, n (%)			
A term (≥ 37 weeks)	27 (90.0)	27 (90.0)	54 (90.0)
Preterm (< 37 weeks)	3 (10.0)	3 (10.0)	6 (10.0)
Father's education, n (%)			
High education level	18 (60.0)	21 (70.0)	39 (65.0)
Low education level	12 (40.0)	9 (30.0)	21 (35.0)
Mother's education, n (%)			
High education level	19 (63.3)	19 (63.3)	38 (63.3)
Low education level	11 (36.7)	11 (36.7)	22 (36.7)
Number of siblings, n (%)			
≤ 2 children	27 (90.0)	26 (86.7)	53 (88.3)
> 2 children	3 (10.0)	4 (13.3)	7 (11.7)
C-reactive protein level, mean (± SD)	2.4 (± 3.7)	1.2 (± 0.6)	1.8 (± 1.0)
Birth weight (kg), median (min-max)	2.8 (1.4–3.9)	2.9 (1.7–4.4)	2.9 (1.4–4.4)
Birth length (cm), mean (± SD)	48.6 (± 1.8)	48.9 (± 2.5)	48.75 (± 2.1)
Weight (kg), median (min-max)	7.9 (5.0–10.0)	8.5 (5.1–12.8)	8.0 (5.0–12.8)
Length (cm), mean (± SD)	70.9 (± 7.1)	74.7 (± 8.3)	73.0 (53.0–92.0)
Body mass index (kg/m^2), mean (± SD)	14.8 (1.9)	15.43 (2.0)	15.14 (1.9)
Weight/age (z-score)	–2.8 (± 1.0)	–0.9 (± 1.0)	–1.9 (± 1.3)
Length/age (z-score)	–3.2 (± 1.1)	–0.7 (± 0.8)	–2.0 (± 1.6)
Weight/length (z-score)	–1.7 (± 2.0)	–1.2 (± 1.6)	–1.4 (± 1.8)

SD: Standard deviation, Kg: Kilo gram, cm: Centimeter, min: Minimal, max: Maximal.

Discussion

Children with congenital heart disease are at increased risk for poor growth, including stunting. Stunting is a major public health problem, especially in poor and developing countries. This study is an observational analytical study with a case-control design, to prove higher CRP levels as a risk factor of stunting in children with acyanotic CHD aged 6–24 months old. Stunting is a form of growth failure (growth faltering) due to the accumulation of insufficient nutrients that lasts for a long time starting from pregnancy until the age of 24 months. Factors that play a role in growth failure in children with CHD are increased caloric requirements and body metabolism, decreased intake (anorexia) due to difficulty in eating and drinking (intermittent eating and drinking), and impaired utilization and absorption of nutrition. Chronic inflammation has an important role in the incidence of stunting in children with acyanotic CHD. In this study, multivariate analysis was performed using binary logistic regression, CRP levels ≥3 mg/dL as a risk factor of stunting in children with acyanotic CHD with p = 0.031 (aOR 22.89; 95% CI 1.32–395.39). Syed *et al*. [8], found that systemic inflammation at 6 weeks of age was significantly associated with stunting (p = 0.002; HR: 2.14, 95% CI 1.23, 3.72). CRP levels increased significantly with a mean of 0.99 ± 0.15 mg/L, with p < 0.001 [8]. Prendergast *et al*. [11] found that increased CRP levels were significantly associated with the incidence of stunting in children (p = 0.008; aOR 3.06; 95% CI 1.34, 6.99) [11].

The c-reactive protein is a marker of systemic inflammation. CRP levels can be elevated in conditions such as congenital heart disease and stunting. CRP levels can be used to indicate the functional status of the heart muscle and cardiac vascular abnormalities in children. Acyanotic congenital heart disease can result in hemodynamic disturbances, such as volume overload or pressure on the heart. These hemodynamic abnormalities lead to activation of

Table 2: Bivariate and multivariate analysis the risk factors of stunting in children with acyanotic congenital heart disease

Characteristic	Stunting		OR (95% CI)[a]	p[#]	aOR (95% CI)[b]	p[+]
	Yes	No				
CRP levels, n (%)			2.15 (0.36–12.76)	0.671*	22.89 (1.32–395.39)	**0.031**
CRP≥3 mg/dL	4 (66.7)	2 (33.3)				
CRP<3 mg/dL	26 (48.1)	28 (51.9)				
Age (months), n (%)			0.41 (0.14–1.22)	0.108	0.21 (0.03–1.24)	0.087
≤12 months	8 (36.4)	14 (63.6)				
>12 months	22 (57.9)	16 (42.1)				
Gender, n (%)			5.50 (1.81–16.68)	**0.002**	10.85 (1.95–60.37)	**0.006**
Male	20 (71.4)	8 (28.6)				
Female	10 (31.3)	22 (68.8)				
Residence. n (%)			1.37 (0.45–4.17)	0.573	13.51 (1.71–106.77)	**0.014**
Rural	22 (52.4)	20 (47.6)				
Urban	8 (44.4)	10 (55.6)				
Gestational age (weeks), n (%)			1.00 (0.18–5.40)	1.000	5.74 (0.34–96.68)	0.225
Aterm (≥37 weeks)	27 (50.0)	27 (50.0)				
Preterm (<37 weeks)	3 (50.0)	3 (50.0)				
Mother's education, n (%)			1.00 (0.35–2.85)	1.000	0.72 (0.10–5.28)	0.752
High education level	19 (50.0)	19 (50.0)				
Low education level	11 (50.0)	11 (50.0)				
Father's education, n (%)			0.64 (0.22–1.87)	0.417	0.61 (0.08–4.37)	0.624
High education level	18 (46.2)	21 (53.8)				
Low education level	12 (57.1)	9 (42.9)				
Number of siblings, n (%)			1.38 (0.28–6.79)	0.688	4.31 (0.26–71.44)	0.308
≤2 children	27 (50.9)	26 (49.1)				
>2 children	3 (42.9)	4 (57.1)				
Birth weight. n (%)			3.50 (1.11–11.01)	**0.028**	61.36 (3.72–1009.91)	**0.004**
≤2500 g	14 (70.0)	6 (30.0				
>2500 g	16 (40.0)	24 (60.0)				
Nutritional status. n (%)			4.03 (1.37–11.83)	**0.010**	27.45 (3.11–241.77)	**0.003**
Under-nutrition	21 (65.6)	11 (34.4)				
No under-nutrition	9 (32.1)	19 (67.9)				

[a]Analisis bivariat, [b]Analisis multivariat, [#]Chi square test, *fisher exact test, [+]regresi logistic biner, CRP: C-reactive protein.

inflammatory cytokines that result in cardiac myocyte damage, fibroblast formation, and vascular endothelial cell dysfunction. This condition results in pathological conditions such as cardiac hypertrophy, fibrosis, and damage to heart cells, thereby reducing heart function [5], [6]. Congenital heart disease can affect the respiratory system and cause diseases, such as recurrent respiratory infections. Congenital anomalies in the heart cause increased blood flow to the lungs, thereby disrupting the pulmonary defense system. This can lead to recurrent respiratory infections in children with congenital heart disease. Infection can increase the inflammatory response [12]. The inflammatory response in the form of activation of macrophages and T lymphocytes releases pro-inflammatory mediators such as TNF-α, IL-1, and IL-6 produced by macrophages. This cytokine will stimulate the formation of the reactant, CRP in the liver. Increased levels of CRP will suppress IGF-1 production, causing a decrease in growth hormone early in life [13]. Interventions that can be done to reduce CRP levels are to provide multivitamins that have anti-inflammatory effects such as antioxidants. Antioxidants are the body's first line of defense against oxidative stress, which has the effect of reducing inflammation. A diet high in antioxidants such as Vitamin C, Vitamin D, and omega 3 can reduce oxidative stress. The anti-inflammatory effect of antioxidants is to suppress the production of cytokines, thereby reducing CRP formation [14], [15], [16].

This study found that the mean age of the study sample was 15.8 ± 6.4 months. In the stunting group, there were more children aged >12 months (73.3%) than children aged 12 months (26.7%). Age was not a significant risk factor for stunting ($p = 0.087$). This study divides the age into less and more than 12 months because children aged more than 12 months will experience the transition of feeding from a soft diet (porridge/team rice) to a solid diet (rice). They tend to be picky eaters, so the nutritional food content is unbalanced. Titaley *et al*. [17] found that children with stunting mostly occur at the age of 12–23 months [17]. Mbuya *et al*. [9] also reported that the difference in child length increased with age from 12 months until the child reached the age of 2 years [9]. Suboptimal growth with age may be related to the feeding transition. With increasing nutritional needs, if a child is not provided with adequate food, linear growth disorders can occur [18], [19]. Increased exposure to various diseases and conditions in children with age, such as food hygiene and environmental sanitation, can also contribute to poor growth [20].

In this study, the percentage of males (66.7%) was higher than females (33.3%) with a ratio of 2:1. This study found that males had a greater risk of stunting 5.5 times higher ($p = 0.002$; 95% CI 0.81–16.68) in children with acyanotic CHD. Titaley *et al*. [17] found that boys had a 33% greater risk of stunting than girls ($p < 0.001$) [17]. Cruz *et al*. [21] found that boys were more likely to have stunting than girls [21]. Physical growth between boys and girls is different. Boys tend to have larger body proportions, are more active and have heavier activity patterns; therefore, they have more nutritional needs. They are more at risk for malnutrition if their nutritional needs are not fulfilled [22]. In this study, most of the subjects with stunting lived in rural areas (73.3%). Children who lived in rural areas had a 13.51 times higher risk of stunting ($p = 0.014$; 95% CI 1.71–106.77). Lestari *et al*. [23] found children who lived in rural areas were more likely to be stunting [23]. This is said because parenting patterns and understanding of nutrition in families who lived in rural areas were lower than in urban areas [9].

Gestational age has an important influence on a child's growth. In this study, 90% of the subjects with stunting were born a term (≥ 37 weeks). Gestational age was not a significant risk factor of stunting ($p = 0,225$). Titaley *et al*. [17] found the gestational age of stunting children was greater in gestational age ≥37 weeks, 68.2% [17]. In this study, children with birth weight ≤2500 g had a risk factor 3.50 times higher of stunting ($p = 0.028$; 95% CI 1.11–11.01). Titaley *et al*. [17] found the risk of stunting in children with birth weight ≤ 2500 g is 2.55 times higher ($p < 0.001$) [17]. This condition was related to the lack of maternal nutrition during pregnancy which causes the supply of food and oxygen to be hampered, resulting in malnutrition in infants as indicated by low birth weight. Babies with low birth weight also had a high risk of being susceptible to diseases that can affect growth [24].

The education level of parents plays an important role in the growth of children. In this study, most of the education levels of fathers and mothers in children with stunting were high (60.0% and 63.3%, respectively). The education level of the mother and father was not a significant risk factor of stunting ($p = 1,000$ and $p = 0.417$). Titaley *et al*. [17] have a different finding. This study found both fathers and mothers had lower education levels [17]. In this study, most children with stunting had ≤2 siblings (90.0%). The number of siblings is not a significant risk factor of stunting ($p = 0.308$). Rufaida *et al*. [22] found most children with stunting have 2 or more siblings (78.5%) [22]. This study is not the same as the research conducted by Titaley *et al*. [17], which found that the incidence of stunting significantly increased in families with more than 2 children ($p = 0.001$) [17]. In this study, under-nutrition increase risk of stunting 4.03 times ($p = 0.010$; 95% CI 1.37–11.83). Cruz *et al*. [21], found there is a significant relationship between chronic under-nutrition and stunting (aOR 4.57; 95% CI 2.06–10.12; $p < 0.05$). Food intake is associated with the incidence of stunting in children.

Optimal nutrition can be achieved by providing nutrients that meet all potential growth needs. Children who are not given good nutrition will be susceptible to growth disorders [21].

The limitations of this study are some of the data are very dependent on the memories of parents which can lead to recall bias and affect the results of the study. Other influencing factors such as food intake and food absorption (maldigestion or malabsorption) which are known from a complete stool examination to see digestive waste were not investigated in this study. The degree of defect in cardiac abnormalities was not differentiated in this study. Children with larger defects are more likely to have recurrent infections. This can affect the results of the study. This study found that CRP levels were significantly higher as a risk factor for stunting, but with a wide range of confidence intervals. This is presumably due to the small number of samples in the study.

Conclusion

This study can prove that higher CRP levels as a risk factor of stunting in children with acyanotic CHD. Other significant risk factors were male, living in rural areas, low birth weight, and under-nutrition.

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