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FULL PAPER

Correlation of vitamin D status, interleukin-6 level, and disease severity in children with pneumonia: A cross sectional study

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Pneumonia is the leading cause of morbidity and mortality among children under five. Recent study found that vitamin D deficiency increased risk of severe pneumonia. Vitamin D regulates the expression of interleukin (IL)-6. Studies about correlation of vitamin D status with IL-6 and disease severity were still limited. The aim of this study was to evaluate the correlation of vitamin D status with IL-6 and disease severity according to the Pediatric Respiratory Severity Score (PRESS) score and World Health Organization (WHO) criteria in children aged 1-60 months with pneumonia. This study was a cross sectional study in children aged 1-60 months with pneumonia at Dr. Soetomo General Academic Hospital Surabaya. Examination of 25-hydroxyvitamin D3, IL-6, and disease severity assessment using PRESS or WHO criteria were performed on the 1st day of hospitalization. The subjects divided into two groups according to 25-hydroxyvitamin D3 level; group 1 (<30 ng/mL) or group 2(≥30 ng/mL). Correlation between variables was performed using Chi-squared test and Mann-Withney U test. Statistical significance was considered as $p < 0.05$. Forty-five children were involved in this study, consisted of 30 (66.67%) boys and 15 (33.33%) girls with median of age 10 (2-60) months. Mean of 25-hydroxyvitamin D3 level was 28.11±8.99 ng/mL. Median of IL-6 level was 47.51 (11.71-468.07) ng/L. Level of 25-hydroxyvitamin D3 had significant negative weak correlation with IL-6 (r_s=-0.357, p=0.017), but did not correlate with disease severity according to PRESS score or WHO criteria. The results of this study showed that vitamin D status is correlated with IL-6 but not disease severity in children aged 1-60 months with pneumonia.

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KEYWORDS

Pneumonia; vitamin D; interleukin-6; PRESS; WHO.

Introduction

Pneumonia was one of the leading causes of morbidity and mortality in children under-five. The incidence of pneumonia in children was estimated at 1 case per 71 children per year, commonly occurred in South Asia, West Africa, and Central Africa [1]. Furthermore, data from 2019 showed that pneumonia caused 740.180 child deaths worldwide [2].

Recent studies showed that vitamin D inadequacy (<30 ng/mL of 25-hydroxyvitamin D3 [25-(OH) D3] level) increased risk of pneumonia and correlate with disease

severity [3-5]. The prevalence of vitamin D inadequacy in children was ranged from 12-61% worldwide [6]. Study in India showed that 38.8% children with pneumonia have vitamin D inadequacy, meanwhile 19% children with pneumonia in Indonesia has vitamin D inadequacy [6,7]. Vitamin D regulates proliferation and differentiation of immune cells, and expression of pro-inflammatory cytokines against infections [8]. One of the most important cytokine related to pneumonia severity and prognosis in children was interleukin-6 (IL-6) [9,10].

Studies regarding correlation of vitamin D status with IL-6 level and disease severity according to Pediatric Respiratory Severity Score (PRESS) and World Health Organization (WHO) criteria is still limited and inconclusive. Previous similar study found a weak negative correlation between 25-OH D3 and IL-6 level in newborn with pneumonia, but another study found a positive very weak correlation in children ages 2-35 months [11,12]. Regarding disease severity, previous study has found a difference of 25-OH D3 level between non-severe pneumonia and severe pneumonia according to WHO criteria but another study denied the results [7,11,13-14].

Vitamin D is cheap and widely available, but the effect on children with pneumonia is still inconclusive. Therefore, further research is needed, particularly on inflammatory markers and disease severity [15]. The 25-(OH) D3-level is hypothesized to be negatively correlated with IL-6 level and disease severity. Thus, this study aimed to assess the correlation between vitamin D status, IL-6 levels, and disease severity, as measured by the PRESS score and WHO criteria, in children aged 1-60 months with pneumonia.

Experimental

This hospital-based cross-sectional study was conducted at Dr. Soetomo General Academic Hospital/Airlangga University Surabaya to evaluate the correlation of vitamin D status with IL-6 level and disease severity of children aged 1-60 months with pneumonia. Children aged 1-60 months diagnosed with pneumonia who admitted to our emergency department were recruited as subjects in this study. The subjects then divided into two groups according to vitamin D status; subject with vitamin D inadequacy (<30 ng/mL of 25-hydroxyvitamin D3 [25-(OH) D3] level) (group 1, n=27) or with normal level of vitamin D (≥30 ng/mL of 25-hydroxyvitamin D3 [25-(OH) D3) (group 2, n=17) [16]. Subjects who already consumed vitamin D3 at least 4 weeks before admission, got antibiotic therapy for more than 3 days before admission, had cyanotic congenital heart disease, renal failure, and post-streptococcal acute glomerulonephritis were excluded.

The outcome of this study was vitamin D status (25-OH D3 level), IL-6 level, and disease severity of pneumonia assessed using PRESS score and WHO criteria. Level of 25-OH D3 and IL-6 was measured on the 1st day of hospitalization. Approximately 3-4 ml of venous blood was obtained from each subject, centrifuged at 3000 rpm for 10 minutes, and stored at -20 °C. Enzyme linked immunosorbent assay (ELISA) was performed to measure 25-OH D3 (25-hydroxyvitamin D3 [25(OH)D] ELISA kit DBC Diagnostic Biochem Canada Inc. [catalog number CAN-VD-510]) and IL-6 level (human interleukin 6, IL-6 Elisa Kit 96T [catalog number E090Hu]). Baseline data (gender, age, weight, and height) and clinical manifestations were also documented. Disease severity was assessed using PRESS score and WHO criteria based on clinical manifestations. Parameters of PRESS score are presence of tachypnea, wheezing, chest retraction, O_2 saturation, and feeding difficulties with each component given a score of 0 or 1. It then categorized as mild (1-2), moderate (3-4), and severe (5-6) [17]. Classification of WHO criteria consists of non-severe pneumonia if there is tachypnea and/or chest retraction, and severe pneumonia if those signs followed by danger

signs (O_2 saturation <90%, central cyanosis, respiratory distress, refuse to drink, vomiting, decrease of consciousness, and seizure) [18].

Categorical variable was presented as proportion and percentages. Continuous variable was presented as mean ± SD for normal distribution data or median (min-max) for skewed data. Correlation analysis was performed using Chi-squared test and contingency coefficient or Spearman's correlation. Comparative analysis was performed using Chi-squared test or Mann-Withney U test. Statistical significance was considered at $p < 0.05$.

Ethics approval was obtained from Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, under no. 0379/KEPK/III/2022.

Results and discussion

A total of 47 subjects involved in this study. Two patients were excluded because incomplete data. Our subject in this study consists of 30 (66.67%) boys and 15 (33.33%) girls with median of age 10 (2-60) months. Majority of our subjects had vitamin D inadequacy (28 [62.22%]), consisted of 9 (20%) subjects with deficiency (<21 ng/mL) and 19 (42.22%) subjects with insufficiency (21-<30 ng/mL). There was no significant difference on baseline characteristics between two groups (Table 1). Level of 25-OH D3 in group 1 was 22.42 ± 4.98 ng/mL and in group 2 was 36.84 ± 6.73 ng/mL.

TABLE 1 Baseline characteristics

Parameters	Group 1 (n=28)	Group 2 (n=17)	*P*- value
Gender*			
Girl	10 (35.7)	5 (29.4)	0.752[a]
Boy	18 (64.3)	12 (70.6)	
Age (month)*	14 (2-60)	10 (2-46)	0.231[b]
Weight (kg)**	8.5 (3.2-16)	6.5 (3.2-11)	0.259[b]
Height (cm)**	70.5 (50-101)	67 (54-98)	0.361[b]
Nutritional status*			
Severely wasted	8 (28.6)	4 (23.5)	
Wasted	3 (10.7)	2 (11.8)	
Normal	11 (57.1)	10 (58.8)	0.702[b]
Overweight	1 (3.6)	1 (5.9)	
Obesity	-	-	
25-OH D3 (ng/mL)***	22.42 ± 4.98	36.84 ± 6.73	-

Data are presented as: *n (%), **median (min-max), ***mean ± SD.
[a]Chi-squared test, [b]Mann-Withney U test.

Correlation analysis between 25-OH D3 and IL-6 level was performed using Spearman's correlation. Mean of 25-OH D3 level was 28.11 ± 8.99 and median of IL-6 level was 47.51 (11.71-468.07) ng/L. Our result showed a significant weak negative correlation between two variables (rs = -0.357, p=0.017). The IL-6 level was significantly higher in subjects with vitamin D inadequacy (p = 0.033) (Table 2). However, no significant correlation was found between disease severity either assessed by PRESS score or WHO criteria with vitamin D status (Table 2).

TABLE 2 Comparison of IL-6 levels and correlation of disease severity between groups

Variable	Group 1 (n=28)	Group 2 (n=17)	C	*P*-value
IL-6 (ng/L)*	53.5 (12.8-468.1)	33.1 (11.7-241.4)	-	0.033[a†]
PRESS**				
Mild	-	-		
Moderate	17 (60.7)	13 (76.4)	0.16	0.277[b]
Severe	11 (39.3)	4 (23.6)		
WHO**				
Non-severe	7 (25.0)	5 (29.4)	0.048	0.746[b]
Severe	21 (75.0)	12 (70.6)		

Data are presented as: *median (min-max), **n (%),
[a]Mann-Withney U test, Chi-squared test, and coefficient contingency, †p<0.05.

We found 28 (62.22%) subjects with vitamin D inadequacy, consisted of 9 (20%) subjects with deficiency (<21 ng/mL) and 19 (42.22%) subjects with insufficiency (21-<30 ng/mL). It was similar with previous study which found 19-22.1% children aged 0-6 years old with pneumonia have vitamin D deficiency [7,19].

Our study showed a significant weak negative correlation between the 25-OH D3 level and the IL-6 level, in accordance with previous similar study conducted in newborn with pneumonia. It found a weak negative correlation between 25-OH D3 and IL-6 level (r_s=-0.345, p=<0.001) [12]. Another study found a significant correlation but in different direction. Level of 25-OH D3 has positive very weak correlation with IL-6 level in children aged 2-35 months with pneumonia (r_s=0.133, p=0.007) [11]. Meanwhile, correlation of those two variables in adult with COVID-19 pneumonia was a significant negative moderate correlation (r_s=- 0.42; p=0.016) [20].

The relationship between two variables was emphasized by comparison of IL-6 levels between groups. Subjects with vitamin D inadequacy had significantly higher IL-6 level than subject with normal status of vitamin D. It was supported by previous studies by Jachvadze *et al.* [21] and Lezhenko *et al.* [22].

The relationship between vitamin D and inflammation is not clearly understood. The weak correlation in our result demonstrates that the 25-OH D3 level is not the only factor that impacts IL-6 level, and IL-6 expression is not influenced only by the 25-OH D3 level.

Vitamin D promotes expression of mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1) that inhibits MAP kinase p38 function. This protein involved in expression of IL-6 [23]. Vitamin D also regulates production of other pro-inflammatory cytokines such as IL-1β, IL-2, tumor necrosis factor-α, and interferon-γ via regulating transforming growth factor β-mediated nuclear translocation mechanism of YAP/TAZ complex [12]. Inadequacy of vitamin D would also increase those pro-inflammatory cytokines. Interleukin-6 expression was also influenced by exercise, and aother micronutrient such as vitamin D, vitamin C, and zinc [24-27].

It could be revised to "Interleukin-6 is considered one of the most important cytokines related to pneumonia severity [9,10]. Interleukin-6 caused injury in endothel and alveolar epithelial cells. Injury to endothel cells promote expression of IL-1 that causes bronchoconstriction and influence appetite center in hypothalamus, leads to feeding difficulties [28,29]. Injury of alveolar epithelial cell causes oxygen diffusion abnormality, leads to tachypnea, retraction, and decreased oxygen saturation [28].

This study found a weak correlation between vitamin D status and IL-6 level, but correlation between vitamin D status and disease severity was not found. Previous observational studies supported the result

that vitamin D status on admission was not correlated with the severity of pneumonia according to WHO criteria [7,11,13]. However, one study found the opposite result [14]. Different criteria used to assess pneumonia severity might lead to different conclusion. Studies that found significant correlation between vitamin D status and disease severity used the researcher's own criteria in their study protocol [12,30-31].

Various conditions might also cause conflicting results with previous studies. Pneumonia severity is influenced by another variable such as gender, malnutrition, breastfeeding, immunization, and exposure to tobacco smoke [14]. The severity of disease is also influenced by comorbidity and the etiology of pneumonia [7]. Different forms of vitamin D measured as a representation of vitamin D status may also cause bias. Previous and current studies use 25-OH D3 levels to determine vitamin D status because they have a longer half-life [32]. Meanwhile, the active form of vitamin D is 1.25-dihydroxyvitamin D3 (1.25-OH_2 D3) [33]. Children with decreased ability to perform hydroxylation of 25-OH D3 into 1,25-OH_2 D3 would have low activity of vitamin D despite classified as normal vitamin D status [4].

Limitations of our study included the relatively small sample size, which might interfere with the power to evaluate the correlation between variables. Our study did not evaluate the etiology of pneumonia which might influence IL-6 level and disease severity. The nature of cross-sectional studies also restricts us from evaluating seasonal variations in 25-OH D3 levels and the etiology of pneumonia.

Conclusion

To sum up, this study found a weak negative correlation between vitamin D status and IL-6 levels, but no correlation was observed with disease severity in children aged 1-60 months with pneumonia. Further randomized controlled trial with larger sample sizes are warranted to confirm the assosiation between 25-OH D3 and IL level in children with pneumonia.

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Authors' Contributions

The authors are contributed to all research processes, including proposal preparation, data collection, data analysis, and final manuscript preparation.

Conflict of Interest

The authors declare that there is no confict of interest in this article.

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