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Vitamin D Insufficiency as Risk Factor of Severe Pneumonia in Children

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Abstract

Severe pneumonia is an infectious disease with high morbidity and mortality in children under five. Several risk factors of severe pneumonia have been established, one of them is vitamin D insufficiency. Risk factors for severe pneumonia can help clinicians to provide better quality of life. This research aimed to prove that vitamin D insufficiency is a risk factor for severe pneumonia in children. This analytical study with case-control design performed in children aged 2 months until 59 months old. Case consisted of 42 subjects who suffered severe pneumonia, while control consisted of 42 subjects who suffered pneumonia. Both groups fulfilled the eligibilities and matched proportionally based on age. The study was conducted from June 2019 to March 2021, level of 25(OH) D was checked in both groups. Data was analyzed by Chi-square test and logistic regression with significant level set at $p<0$, 05. Total eighty-four subjects with median age 11, 5 month were included in this study and most of them were male (59, 5%). The risk factors of severe pneumonia was vitamin D insufficiency with *adjusted odds ratio* 4.71 (CI95% 1.15-19.31, p=0.031) and exposure of cigarette smoke with *adjusted odds ratio* 5.19 (CI95% 1.76-15.31, p=0.003). There was no association of gender, mild malnutrition, non-exclusive breastfeeding and incomplete immunization in this study. Vitamin D insufficiency is a risk factor for severe pneumonia in children.

Keywords: Severe pneumonia; Vitamin D insufficiency; Risk factor; Children

1. Introduction

Pneumonia is an infectious disease that is the main cause of death in children under five worldwide. The incidence of pneumonia diagnosed based on clinical symptoms occurs in developing countries around 150.7 million new cases per year and11-20 million or 7-13% occurs in as severe pneumonia that required hospitalization. To date, in developed countries there is no comparable data available. However, population-based research reported that the incidence of pneumonia among children less than five years old showed more than 95% occurs in developing countries [1].

The incidence of pneumonia increases yearly, according to data from Indonesian health profile 2016, the incidence of pneumonia based on recalled memory of having been diagnosed with pneumonia by health workers in previous month before the survey on infants in Indonesia from the last few years since 2014 ranging was 20-30%. In 2015 there was an increase, 63.45% of cases and in 2016 it increased into 65.27% [1].

It is estimated that there were 1,346 pneumonia patients in Denpasar and 1,352 patients were treated (100.43%). The Health Department of Bali Province estimated the number of pneumonia cases that occur in children under five was 2.05% from total number of children under five[2].

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Currently there are no preventive therapy for pneumonia, so treatment depends on the presenting symptoms. The high impact of pneumonia on economy requires a method to reduce the risk of infection and mortality at low cost. The status of immune system is influenced by many factors that contribute to the risk of infection-related mortality and morbidity [3]. Several micronutrients have been reported to play role in the process of immunological responses in pneumonia patients, but the role of vitamin D is still being studied to present [4-5]

Vitamin D regulates macrophages in phagocytosis and relies on antibodies that protect against respiratory tract infections. Moreover the active vitamin D produce enzyme namely 1α-hydroxylase, is found in respiratory epithelial cells, alveolar macrophages, dendritic cells and lymphocytes. These findings suggest that active vitamin D can be produced in the lungs [6].

There are different implications of terms related to vitamin D insufficiency and vitamin D deficiency to the severity of pneumonia, but the clinical differences are still not conclusive. Vitamin D deficiency can significantly increase the incidence of severe pneumonia or sepsis, but by implication the incidence of vitamin D insufficiency can also increase the severity of disease (eg severe pneumonia), bacteremia and high mortality [7-8]. A research [9] using cut-off value <30 ng/ml reported that in patients with severe pneumonia, vitamin D deficiency was strongly associated with neutropenia and hypoxia (oxygen saturation less than 88%). Several studies using cut-off point of vitamin D below 20 ng/ml found significant relationship to the severity of pneumonia [10], and another study [11] stated that the mean level of serum 25(OH) D was 22.69±9.56 ng/ml and significant related to the degree of pneumonia. In addition there are several other risk factors for pneumonia in children, such as history of non-exclusive breastfeeding[12], exposure of cigarette smoke[13] nutritional status, incomplete immunization, age under 1 year[14]

Based on the background of the problem above and the incidence data of vitamin D insufficiency in patients with severe pneumonia in Indonesia does not exist, thus encouraging researchers to conduct and prove that vitamin D insufficiency is a risk factor for severe pneumonia

2. Material and methods

This research was an observational analytic study, used case-control design by matching both groups based on age. The study began by determining the diagnosis, namely pneumonia, then divided into two groups. A case group, consisted of children who were treated with severe pneumonia and a control group, consisted of children who were treated with pneumonia. Then the vitamin D levels were analyzed. The research was carried out in Sanglah Central General Hospital, Wangaya Regional General Hospital and Udayana University Hospital from June 2019 to March 2021 in pediatric patients aged 2 months - 59 months old diagnosed with pneumonia and severe pneumonia.

Samples were collected by consecutive sampling that meet the inclusion criteria such as: children aged 2 months to 59 months with pneumonia and severe pneumonia, parents agreed and signed informed consent after explanation. Exclusion criteria was children with any of the following condition: malignancy disease, congenital heart disease, chronic kidney disease, poor nutritional status, chronic liver disease, HIV.

Sample size was counted by using formula for paired case-control study formula, Type one error was set at 5%, alpha standard value 1.96, type two error 20%, P 0.65 based on literature[8], Odds ratio 1.84, finally we got the minimal sample were 84 subjects.

The independent variable in this study was vitamin D insufficiency, dependent variable was severe pneumonia. In addition variables controlled by design were malignancy diseases, congenital heart disease, chronic kidney disease, malnutrition, chronic liver disease and variables controlled by analysis were gender, nutritional status, history of exclusive breastfeeding, history of immunization, history of exposure to cigarette smoke.

Data was analyzed by using computer program in bivariate analysis to assess the risk of vitamin D insufficiency, gender, malnutrition, non-exclusive breastfeeding, incomplete immunization and exposure of cigarette smoke for severe pneumonia using the chi-square test. The level of significant was set with p value <0.05. Then multivariate analysis was performed on variables that had p-value <0.25 in bivariate analysis. Then analysis was performed by using logistic regression test.

This research has obtained ethical clearance from the Research Ethics Commission, Faculty of Medicine, Udayana University/Sanglah Hospital No: 2557/UN14.2.2.VII.14/LP/2019 as well as research permit at Sanglah Hospital Denpasar Number: LB.02.01 /XIV 2.2.1/0495/2020, research permit at Wangaya Hospital Number: 070/663/RSUDW, as well as permit from the Investment Agency and One Stop Integrated Service Number: 070/09736/DPMPTSP-B/2019.

3. Results

This research was conducted at Sanglah Hospital with 65 samples, Wangaya Hospital with 17 sample and Udayana University Hospital with 2 samples from June 2019 to March 2021. During the study period there were 261 children who met pneumonia criteria. In addition 51 children were excluded due to malignancy, 70 children due to congenital heart disease, 3 children due to chronic kidney disease, 35 children due to malnutrition, 10 children due to chronic liver disease, and 8 children due to HIV (figure 1).

Median age was 11.5 months (range 2 months to 59 months), median length of stay was 5 days (range 3-16 days). The average vitamin D level in this study was 23.81±10.90 ng/mL, most of the subjects were dominated by men (59.5%). The characteristics of the research subjects can be seen in the table below (table1).

Data showed severe pneumonia in subjects with vitamin D insufficient levels was 39 (92.9%) and in subjects with vitamin D sufficient levels as much as 3 (7.1%) (table 2).

In Table 3 other risk factors that are confounding factors in this study such as gender, nutritional status, non-exclusive breastfeeding, incomplete immunization and exposure to cigarette smoke were analyzed by using chi square and presented as odd ratio (OR) with confidence interval (CI) 95%. In this study, there was no association between male gender and history of incomplete immunization with severe pneumonia. Meanwhile poor nutritional status, not getting exclusive breastfeeding and exposure to cigarette smoke are related so therefor multivariate analysis was carried out.

In Table 4 multivariate analysis was conducted to determine the relationship between vitamin D insufficiency and severe pneumonia after taking into account the confounding variables, namely male gender, malnutrition, not exclusive breastfeeding, incomplete immunization and exposure to cigarette smoke.

Based on the data presented in table 4, the effect size displayed based on the B coefficient indicates that vitamin D insufficiency variable has significant value as risk factor for severe pneumonia in children. Children with vitamin D insufficiency had risk 4.71 times greater for the occurrence of severe pneumonia (95%CI 1.15-19.31). After adjustment using multivariate analysis, it was found that exposure to cigarette smoke also affected the occurrence of severe pneumonia with adjusted OR value 5.19 (95%CI 1.76-15.31). Other risk factors, namely male gender, poor nutritional status, non-exclusive breastfeeding and incomplete immunizations are not risk factors for severe pneumonia.

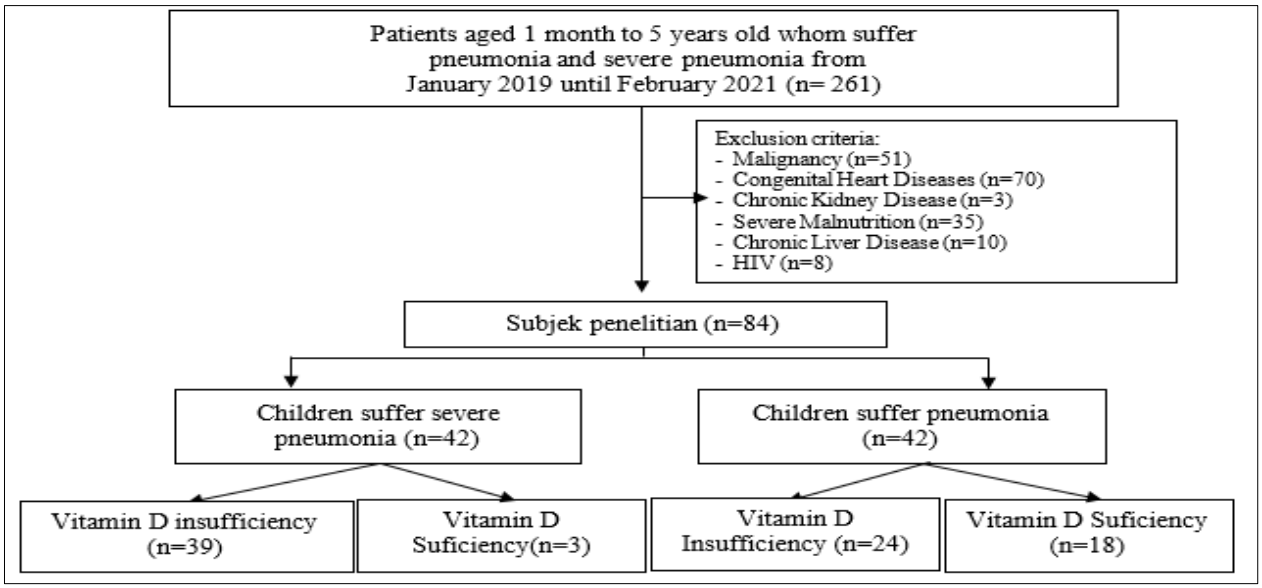

Figure 1 Schematic of result

Table 1 Characteristic of samples

Characteristic	Total n=84	Severe Pneumonia n = 42	Pneumonia n = 42
Age, n (%)			
2 - 12 months old	42 (50.0)	21 (50.0)	21 (50.0)
>12 - 59 months old	42 (50.0)	21 (50.0)	21 (50.0)
Gender, n (%)			
Male	50 (59.5)	22 (52.4)	28 (66.7)
Female	34 (40.5)	20 (47.6)	14 (33.3)
Nutritional status, n (%)			
Malnutrition	29 (34.5)	19 (45.2)	10 (23.8)
Well Nourish	48 (57.1)	18 (42.9)	30 (71.4)
Overweight	3 (3.6)	2 (4.8)	1 (2.4)
Obese	4 (4.8)	3 (7.1)	1 (2.4)
Exclusive breastfeeding, n (%)			
No	39 (46.4)	24 (57.1)	15 (35.7)
Yes	45 (53.6)	18 (42.9)	27 (64.3)
History of vaccination n (%)			
Incomplete	8 (9.5)	6 (14.3)	2 (4.8)
Complete	76 (90.5)	36 (85.7)	40 (95.2)
Exposure of cigarette smoke, n (%)			
Yes	33 (39.3)	26 (61.9)	7 (16.7)
No	51 (60.7)	16 (38.1)	35 (83.3)
History of delivery, n (%)			
Spontan delivery	53 (64.1)	27 (64.3)	26 (61.9)
Pervaginam device assisted	2 (2.4)	2 (4.8)	0
Sectio cesarea	29 (34.5)	14 (33.3)	15 (35.7)
Father's educational degree, n (%)			
Junior High School	6 (7.1)	4 (9.5)	2 (4.8)
Senior High School	46 (54.8)	26 (61.9)	20 (47.6)
Diploma	18 (21.4)	8 (19.0)	10 (23.8)
Bachelor degree	14 (16.7)	4 (9.5)	10 (23.8)
Mother's educational degree, n (%)			
Elementary School	4 (4.8)	2 (4.8)	2 (4.8)
Junior High School	20 (23.8)	14 (33.3)	6 (14.3)
Diploma	9 (10.7)	8 (19.0)	1 (2.4)
Bachelor degree	6 (7.1)	4 (9.5)	2 (4)

Table 2 Distribution of vitamin D based on pneumonia severity

Variable	Severe pneumonia n = 42	Pneumonia n = 42	OR (CI 95%)	p-value
Vitamin D insufficient, n (%)	39 (92.9)	24 (57.1)	9.75 (2.59-36.63)	<0.001
Vitamin D sufficient, n (%)	3 (7.1)	18 (42.9)		

Table 3 Bivariate analysis of risk factor for the severity of pneumonia

Variables	Severe Pneumonia n = 42	Pneumonia n = 42	OR (CI 95%)	p-value
Male gender, n (%)	22 (52.4)	28 (66.7)	0.55 (0.23-1.33)	0.182
Malnourished, n (%)	19 (45.2)	10 (23.8)	2.64 (1.03-6.73)	0.039
Not exclusive breastfed, n (%)	24 (57.1)	15 (35.7)	2.40 (0.99-5.77)	0.049
Incomplete vaccination, n (%)	6 (14.3)	2 (4.8)	3.33(0.63-17.57)	0.137
Exposure of cigarette smoke n (%)	26 (61.9)	7 (16.7)	8.12(2.92-22.59)	<0.001

Table 4 Multivariate analysis of risk factors that influenced severe pneumonia

Variable	*Adjusted* OR	CI 95%	p-value
Vitamin D insufficiency	4.71	1.15-19.31	0.031
Male gender	0.75	0.26-2.18	0.603
Malnourished	1.78	0.58-5.43	0.312
Not exclusive breastfeeding	1.56	0.54-4.53	0.410
Incomplete vaccination	3.07	0.46-20.43	0.244
Exposure of Cigarette smoke	5.19	1.76-15.31	0.003

4. Discussion

This study obtained 84 subjects consisting of 42 subjects with severe pneumonia and 42 subjects with pneumonia. The median age of the patients was 11 months (minimum age 2 months and maximum 59 months). A report data stated that the highest prevalence of pneumonia was found in the age group 1 month to 4 years as much as 2.1%, followed by ages 5-14 years as much as 1.7% and ages 15-24 years as much as 1.8% [15]. In addition, Hoang et al. (2019) also stated the highest prevalence of pneumonia was found in the age group 2 months - <12 months as much as 80.7%, followed by the age group 12-24 months as much as 15.7%, age 34-36 months as much as 1.2%, and 36-59 months as much as 2.4%[16].

Sunyataningkamto et al. stated that 52% of children whom suffering pneumonia were dominated by children aged < 1 year [17]. This may be due to the fact that children aged <1 year have smaller respiratory tract diameters, making them easy to suffer respiratory infections such as pneumonia and if the inflammation becomes widespread, it will increase the risk of respiratory tract obstruction which can lead to hypoxia. In addition, pneumonia that occurs in children aged > 1 year may be due to playing outdoor so they are prone to be exposed to pneumonia-causing agents. Based on population-based cohort analysis conducted by comparing the risk of long-term respiratory morbidity up to the age of 18 years according to gender, it was found that male gender 1.32 times (6.4%) risky for respiratory morbidity, specifically pneumonia, bronchitis and asthma compared with women (4.9%)[18].

Another similar study in Brazil stated the prevalence of pneumonia in men was 52.3%, this may be explained boys more susceptible to pneumonia and because boys play outdoor more often, making them easier to be exposed to infections from environment than girls [14].

In this study, the distribution of male subjects (59.5%) was more than female (40.5%). Women have better immune system than men. In addition, the diameter of respiratory tract in men is smaller during the early years of life, therefore it can affect the occurrence of lower respiratory tract infections [19].

Nutritional status is often associated with body's immune response. Malnutrition is an important risk factor in determining the risk of a child being susceptible to disease and usually most often affects children under the age of 5 years. Undernourished children can develop immunodeficiency, making them susceptible to diseases including

pneumonia, thereby increasing the risk of death among children with pneumonia. Vice versa, children who suffer from pneumonia can experience nutrient loss so that it will impair their immunity [20-21].

In this study, nutritional status was dominated by malnutrition (34.5%) in case group and in control group. Malnutrition causes imbalance in production of antibody, decrease lymphocytes, complement production, immunoglobulin A, interferon, T cells and interleukin receptors. These conditions affect the body's general response to infection, thereby causing higher risk of suffering more severe infections [22]

Currently, there are no findings regarding vitamin D insufficiency on the severity of pneumonia, but several studies have found link between vitamin D deficiency and severe pneumonia. Vitamin D deficiency is associated with 13-fold increased risk of pneumonia in Ethiopian children younger than 5 years[23]. A similar study as above conducted in China with case-control design reported the mean serum concentration of 25(OH)D in pneumonia group was 19.04±9.86ng/mL and 31.71±14.82ng/mL in control group which was significant different ($p<0.001$). Another case-control study conducted in Bali proved that vitamin D deficiency was a risk factor for lower acute respiratory infections compared to controls (RO=5.82; 95% CI 1.706-19.886, p=0.005)[10].

In this study, it was proved that there was significant relationship between vitamin D insufficiency and severe pneumonia in children (p=0.031). Vitamin D insufficiency will increase the risk of severe pneumonia 4.71 times compared to sufficient. This is because vitamin D has important role in innate immune response, by increasing the production of defense agents (antimicrobial peptide) catelicidin. Therefore reduced levels of vitamin D can be a risk factor for pneumonia.

Other variables that are also associated with severe pneumonia in children include gender, poor nutrition, non-exclusive breastfeeding, incomplete immunization and exposure of cigarette smoke. In this study, based on multivariate analysis using stepwise, it was found that in addition to vitamin D insufficiency, the variable exposure to cigarette smoke was also significantly associated with the severity of severe pneumonia in children. Several studies have proven significant relationship between exposure of cigarette smoke and severe pneumonia in children. Exposure of cigarette smoke reduced ciliary movement in respiratory tract, mucus hypersecretion or submucosal gland hypertrophy and squamous cell metaplasia, this is caused by exposure to cytotoxic cigarette smoke that irritate respiratory epithelial cells. Exposure of cigarette smoke has also been reported to increase epithelial permeability through changes in structural integrity of tight junctions as result of decreased expression of genes encoding junctional proteins. In addition, exposure of cigarette smoke also inhibits epithelial cells from producing antimicrobial/antiviral peptide, human -defensin-2. A mismatch of immune responses to influenza virus infection, respiratory syncytial virus (RSV) and rhinovirus with increased viral replication and decreased production of antiviral interferon (IFN)-γ and T lymphocytes[24].

Moreover research stated that history of exposure to cigarette smoke increase risk 3.87 times causing severe pneumonia in children less than 5 years old (95% CI 1.62-9.23; p=0.008)[16]. Another similar study found that children who were exposed to indoor cigarette smoke either during infancy or childhood were at increased risk for respiratory distress (adjusted OR 1.23; 95% CI 1.03-1.47) [25]. Feldman and Anderson stated that prolong exposure to cigarette smoke inhibit the phagocytic activity of respiratory tract pathogens such as S. Pneumoniae, Haemophilus influenzae, and Pseudomonas by alveolar macrophages [24]. In this study, the risk of severe pneumonia increased 5.19 times due to history of exposure to cigarette smoke (adjusted OR 5.19; CI 95% 1.76-15.31).

5. Conclusion

This study proved that vitamin D insufficiency as risk factor for severe pneumonia in children aged 2 months-59 months old. In addition this study also found that exposure of cigarette smoke is a risk factor for severe pneumonia, but the operational definition of exposure to cigarette smoke in this study is still superficial.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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