Zeynep Kamil Med J 2023;54(4):203–208
DOI: 10.14744/zkmj.2023.68094

ORIGINAL ARTICLE

Investigation of subclinical Vitamin D deficiency and other risk factors in community-acquired pneumonia in children

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ABSTRACT

Objective: This study aimed to investigate subclinical Vitamin D deficiency and other risk factors in community-acquired pneumonia in children. In addition to the known infectious causes of pneumonia, we wanted to examine whether Vitamin D deficiency, which can change the characteristics of the immune system, is a risk factor for the disease.

Material and Methods: Ethical approval and study done at Istanbul Medeniyet University Göztepe Training and Research Hospital Pediatric Clinic. Fifty-seven hospitalized patients with the diagnosis of pneumonia and 57 healthy controls were chosen for the study. Patients who have an underlying disease were excluded, and groups were compared. Informed consent was obtained, a questionnaire was prepared for the patients including patients' demographic, familial, and socioeconomic characteristics, possible factors that may cause pneumonia were questioned. Measurements on a digital scale, infantometer, and stadiometer were used. The measurement of 25(OH)-D3 was performed by the chemiluminescence method in an immunoassay.

Results: The age range was 27.89–26.21 months. In the patient group, the number of individuals living in the same house was higher (n:5.35±2.69 vs. n:4.11±0.86; p=0.002), the birth weights of subjects (3117.36±390.80 gr vs. 3340.63±501.71 gr; p=0.010), and serum 25(OH)-D3 levels (25.21±13.19 ng/mL vs. 31.97±12.08 ng/mL; p=0.005) were lower compared to the control group. Illiterate mothers in the patient group (21.1% vs. 0.0%; p=0.001) and mothers who graduated from high school in the control group (8.8% vs. 28.1%; p=0.016) were significantly higher. Serum 25(OH)-D3 levels were 25.21±13.19 ng/mL in the patient group and 31.97±12.08 ng/mL in the control group, showing a statistically significant difference between the groups. In the patient group, the mean serum 25(OH)-D3 levels were significantly low (p=0.005). Vitamin D insufficiency was present in 68.42% of the patients.

Conclusion: In addition to the modifiable risk factors in pneumonia patients, adding Vitamin D supplementation to standard treatment, if necessary, may be effective in reducing the morbidity and mortality of the disease.

Keywords: Children, community-acquired infections, pneumonia, vitamin D, vitamin D deficiency, 25(OH)-D3.

Cite this article as: Öztürk N, Ergüven M, İşbilen Başok B, Aydın E. Investigation of subclinical Vitamin D deficiency and other risk factors in community-acquired pneumonia in children. Zeynep Kamil Med J 2023;54(4):203–208.

Received: February 08, 2023 **Revised:** April 20, 2023 **Accepted:** May 17, 2023 **Online:** October 04, 2023
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INTRODUCTION

Pneumonia is a leading cause of morbidity and mortality during childhood, especially in developing countries. Primary prevention necessitates a thorough assessment of risk factors contributing to childhood pneumonia in addition to vaccination.[1] According to the World Health Organization, pneumonia affects 156 million children under five every year, with an additional 20 million instances of severe pneumonia necessitating hospitalization. Young age, prematurity, low birth weight, no breastfeeding, low socio-economical level, crowded living conditions, malnutrition, inadequate immunization, underlying diseases, and Vitamin D deficiency are predisposing factors for pneumonia. Malnutrition and a lack of access to health services are the most important risk factors that increase mortality.[2–5]

Vitamin D is a fat-soluble vitamin that is necessary for bone development and calcium-phosphorus homeostasis. Moreover, in recent years, it has been shown that Vitamin D regulates lots of genes related to cell proliferation, differentiation, apoptosis, and angiogenesis. It is understood that nuclear Vitamin D receptors are found in many tissues, like myocardia, the brain, the prostate, the breast, the lung, the colon, and immune cells. 1-α hydroxylation of 25(OH)-D is done locally not only in the kidney but also in many tissues like the skin, colon, monocytes, macrophages, and epithelial cells of the respiratory tract.

While it is known that Vitamin D deficiency causes rickets during childhood. Children should currently reach a serum 25(OH)-D concentration of at least 20 ng/mL, according to the American Academy of Pediatrics and the Institute of Medicine. This "threshold" is mostly based on the scientific literature for rickets prevention or treatment.[6] In recent years, it is shown that subclinical Vitamin D deficiency causes infectious, autoimmune, and cardiovascular diseases, obesity, depression, impaired glycemic index, COVID-19, and various types of cancer.[7–10]

Vitamin D2 (ergocalciferol) and Vitamin D3 (cholecalciferol) are the two major isoforms. Ergosterol is converted to Vitamin D3 by UVB light. Vitamin D (both Vitamin D2 and D3), which is obtained from the diet or the skin, connects directly to the Vitamin D-binding protein and travels first to the liver. Vitamin D is converted by the enzymes CYP2R1 and CYP27A1 in the liver to 25(OH)-D (calcidiol), which is the main form of Vitamin D seen in serum. The kidney's proximal tubule is where 25(OH)-D is further converted by 25(OH)-D 1-α-hydroxylase (CYP27B1) to 1,25-dihydroxyvitamin D (1,25[OH]2D, calcitriol), a physiologically active form of Vitamin D.[10] Active Vitamin D inhibits the T-helper 1 cell response, maturation of dendritic cells, differentiation of B cells into plasma cells, and immunoglobulin production. By decreasing proinflammatory cytokine production and stimulating anti-inflammatory cytokine production, it contributes to the control of inflammation.[11]

When toll-like receptors in monocytes and macrophages are activated by microbial agents, expression of Vitamin D receptors and active Vitamin D synthesis in these cells are increased. TLR 2/1's interaction with the precursor of Vitamin D (25(OH)-D) induces the production of the antimicrobial protein cathelicidin.[12] Active Vitamin D contributes to the killing of intracellular bacteria through cathelicidin mRNA induction. Furthermore, active Vitamin D increases the synthesis of S-100 proteins and calprotectin, which are important regulators of the innate immune system.[13] Vitamin D status should be determined by measuring serum 25(OH)-D concentrations. Among the various forms of Vitamin D, serum 25(OH)-D is a good indicator of Vitamin D status and stores. 25(OH)-D is the main circulating form of Vitamin D and has a half-life of 2–3 weeks. In contrast, 1, 25-dihydroxyvitamin D (1,25[OH]2D) has a much shorter half-life of approximately 4 h, circulates in much lower concentrations than 25(OH)-D, and is susceptible to fluctuations induced by parathyroid hormone in response to subtle changes in calcium concentrations.[14]

Studies have shown that Vitamin D deficiency increases the risk of tuberculosis, otitis media, influenza, and upper and lower respiratory tract infections.[15,16] In addition to the known virulent and bacterial causes of pneumonia, we wanted to examine whether Vitamin D deficiency, which can change the characteristics of the immune system, is a risk factor for the disease.

In studies, normal values of serum 25(OH)-D levels vary broadly above 10–30 ng/mL, and experts agree that Vitamin D deficiency should be defined as a 25(OH)-D level of <20 ng/mL. Vitamin D insufficiency is currently recognized as a 25(OH)-D of 21–29 ng/mL, and ≥30 ng/mL is accepted as normal.[17]

In this study, we aimed to examine whether there is an effect of Vitamin D deficiency or insufficiency besides the definitions of risk factors for community-acquired pneumonia.

MATERIAL AND METHODS

This study was done in two groups. The first group (patient group or pneumonia group) was pneumonia cases between the ages of 1 month and 7 years who were inpatients in infant and child services and voluntarily participated in the study. The diagnosis of pneumonia was made clinically (fever, cough, tachypnea, dyspnea, rales, reduction of respiratory sounds, hearing of bronchial voices at the periphery of the lung, the existence of pleural rub), and radiological tests were done in necessary cases. Patients who have an underlying disease that creates a predisposition to infection (chronic renal failure, nephrotic syndrome, primary or secondary immune deficiency, congenital respiratory tract malformation, cystic fibrosis, bronchiectasis, chronic lung disease, congenital heart disease), patients using immunosuppressive drugs or steroids, patients who have malnutrition, obese patients, and inpatients with the diagnosis of pneumonia but have a history of <5 days of hospitalization were excluded from the study. Children were excluded from the study with a history of preterm birth. The patients chosen for the study were all full-term.

In the second group (the control group), children with similar characteristics who were referred to an outpatient clinic for healthy child follow-up and do not have acute or chronic disease and volunteer to participate in the study from 1 month to 7 years of age were included.

We accepted that 25(OH)-D ≤10 ng/mL is Vitamin D deficiency, between 10 and 30 mg/dL is insufficiency, and ≥30 ng/mL is normal.

Informed consent was obtained from the parents of the patients and controls before the study. This study was done at Istanbul Medeniyet University's Göztepe Training and Research Hospital Pediatrics Clinic.

A questionnaire was prepared for the patients included in the study. In the questionnaire, patients' demographic, familial, age of mother, maternal education level, state of being fully vaccinated,

Table 1: Comparison of the groups in terms of risk factors of pneumonia

	Groups				p
	Patient (n=57)		Control (n=57)		
	n	%	n	%	
Number of siblings, Mean±SD (Median)	1.28±1.25 (1.00)		0.84±0.84 (1.00)		**0.082**
Number of individuals living at home, Mean±SD (Median)	5.35±2.69 (5.00)		4.11±0.86 (4.00)		**0.002****
[a]Birth weight (kg), Mean±SD (Median)	3117.36±390.80		3340.63±501.71		**0.010***
Exclusive breastfeeding (month), Mean±SD (Median)	4.84±2.73 (5.75)		5.07±2.29 (6.00)		**0.377**
[b]Age of mother					
30 years and under	32	56.1	34	59.6	**0.850**
Over 30 years	25	43.9	23	40.4	
Maternal education level					
[b]Illiterate	12	21.1	0	0.0	**0.001****
[b]Primary school	29	50.9	27	47.4	**0.851**
[b]Secondary school	9	15.8	8	14.0	**1.000**
[b]High school	5	8.8	16	28.1	**0.016***
[c]University	2	3.5	6	10.5	**0.271**
[b]Mothers' smoking situation	13	22.8	9	15.8	**0.476**
[c]State of being fully vaccinated	55	96.4	57	100	**0.496**
[b]History of previous hospitalizations	26	45.6	17	29.5	**0.082**
[b]History of previous operations	11	19.3	6	10.5	**0.293**

a: Student t-test; b: Yates test; c: Fisher's exact test; *: P<0.05; **: P<0.01; SD: Standard deviation.

mothers' smoking situation, history of previous operations and hospitalizations, and possible factors that may cause pneumonia were questioned. Information was taken from the patients' mothers or fathers through the face-to-face interview method.

Height and weight measurements of the patients and controls were performed by one person with the same instruments. For the measurements, a digital scale, infantometer, and stadiometer were used. The heights of patients up to 2 years of age were measured in supine position with an infantometer; the heights of patients >2 years of age were measured in standing position with a stadiometer. Measurements were also recorded in the questionnaire.

Our study was done in the spring, and patient and control groups were collected in a short time, within 3 months (March, April, and May).

Between the dates specified, 60 hospitalized patients and 58 healthy children who were suitable for the accession criteria of the study were chosen. Three patients in the patient group and one patient in the control group who had inadequate serum samples for 25 (OH)-D were excluded from the study. All the patients were preschool children predisposed to pneumonia as an age group.

After 8–12 h of fasting, venous blood samples were taken from patients for serum 25(OH)-D levels. The blood samples were centrifuged for 10 min at 1500 g for a maximum of 60 min, and serums were stored at -80°C until analysis. Measurement of 25(OH)-D was performed by the chemiluminescence method at the Architect i2000sr immunoassay analyzer (Abbott Laboratories, IL, USA). The measuring range of the test was from 0 to 160 ng/ mL, and the detection limit was 3.1 ng/mL.

For statistical analysis, the number cruncher statistical system, 2007 power analysis and sample size, and 2008 statistical software (Utah, USA) programs were used. Data were analyzed using descriptive statistical methods (mean, standard deviation, median, frequency, rate), and the Student's t test was used for comparisons between groups of parameters showing normal distribution. Kruskal–Wallis test was used for the comparisons between groups of parameters not showing a normal distribution. The Mann–Whitney U Test was used for the evaluation of the groups and the detection of the groups that lead to differences. The chi-square test, Yates continuity correction, and Fisher's exact test were used for the comparison of qualitative data. The value of p<0.05 was accepted as significant.

RESULTS

54.4% of the patients hospitalized for pneumonia were male (n=31), and 45.6% of them were female (n=26). The age of the patients ranged from 1.5 months to 84 months and had a mean of 27.89±26.21 months.

Table 2: Demographic characteristics and 25 (OH) D_3* levels

	Study group (n=57)	Controls (n=57)	p
Age (month), Mean±SD	27.89±26.21	23.25±17.75	0.271[a]
Height (cm), Mean±SD	84.58±21.40	83.73±13.81	0.803[a]
Weight (kg), Mean±SD	12.19±6.34	11.55±3.69	0.510[a]
Gender, n (%)			0.349[a]
Male	31 (54.4%)	26 (45.6%)	
Female	26 (45.6%)	31 (54.4%)	
25 (OH) D_3* (ng/mL), Median (min–max)	20.80 (6.30–73.50)	30.20 (10.40–66.30)	<0.001[b,c]

a: Student t-test; b: Mann-Whitney U test; c: Statistically significant at 0.95 confidence level; *: 25-hydroxyvitamin D_3 (25(OH) D_3); SD: Standard deviation.

45.6% of the cases in the control group were male (n=26), and 54.4% of them were female (n=31). The age of the controls ranged from 3 months to 65 months and had a mean of 23.25±17.75 months.

There was no significant difference between the patient and the control groups in terms of gender or age (p>0.05).

As the groups were compared in terms of risk factors for pneumonia, the number of individuals living at home, birth weight, mothers who were illiterate, and mothers who graduated from high school showed significant differences (p<0.05). The number of individuals living at home was relatively higher in the patient group than in the control group, with mean values of 5.35±2.69 and 4.11±0.86, respectively (p<0.01). The birth weights of the patients were found to be significantly low (p<0.05). In the patient group, the rate of mothers who were illiterate was found to be significantly high (p<0.01). In the control group, the rate of mothers graduated from high school was significantly high (p<0.05) (Table 1).

96.4% of cases in the patient group and all cases in the control group were fully vaccinated according to the Ministry of Health's immunization program.

The duration of exclusive breastfeeding ranged from 0 to 15 months (mean 4.84±2.73 months) in the patient group, and it ranged from 0 to 12 months (mean 5.07±2.29 months) in the control group.

In the patient group, 56.1% of the mothers (n=32) were 30 years old or younger, and 43.9% of the mothers (n=25) were over 30 years old. In the control group, 59.6% of mothers (n=34) were 30 years old or younger, and 40.4% of mothers (n=23) were over 30 years old.

The mean number of siblings in the patient group was 1.28±1.25, while in the control group, it was 0.84±0.84 (p>0.05).

The smoking status of mothers was questioned in terms of passive smoking. 22.8% of the mothers (n=13) in the patient group and 15.8% of the mothers (n=9) in the control group were smokers.

Number of siblings, duration of exclusive breastfeeding, age of the mothers, mothers' smoking situation, state of being fully vaccinated, history of previous hospitalizations, and history of previous operations showed no significant differences (p>0.05). Mothers' education level of being primary school, secondary school, or university degree, did not show a statistically significant difference among the groups (p>0.05) (Table 1).

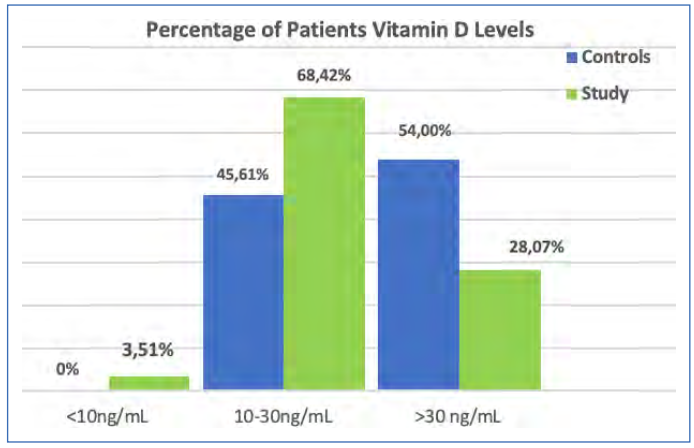

Figure 1: Percentage of patients and mean serum Vitamin D value.

It was found that the mean serum 25(OH)-D levels were 25.21±13.19 ng/mL in the patient group and 31.97±12.08 ng/mL in the control group. The mean serum 25(OH)-D levels showed a statistically significant difference between the groups. In the patient group, the mean serum 25(OH)-D levels were significantly low (p=0.005) (Fig. 1 and Table 2).

As the 25(OH)-D levels were classified, 3.51% (n=2) of the patients had 25(OH)-D levels ≤10 ng/mL, 68.42% (n=39) of the patients had levels between 10 ng/mL and 30 ng/mL, and 28.07% (n=16) of the patients had levels higher than or equal to 30 ng/mL (Fig. 1).

In the control group, it was observed that none of the patients had 25(OH)-D levels ≤10 ng/mL, 45.61% (n=26) of the patients had 25(OH)-D levels between 10 and 30 ng/mL, and 54.39% (n=31) of the patients had 25(OH)-D levels higher than or equal to 30 ng/mL (Fig. 1).

When the Vitamin D levels in the patient group were evaluated, Vitamin D deficiency was obvious in 3.51% of the patients, and Vitamin D insufficiency was present in 68.42% of the patients. 28.07% of the patients had ≥30 ng/mL, which was adequate.

In the control group, 45.61% of the patients had Vitamin D insufficiency. 54.39% of the patients with 25(OH)-D levels ≥30 ng/mL were found to be adequate. There were no cases of overt Vitamin D deficiency in the control group.

DISCUSSION

Indoor and crowded living conditions increase the incidence of the disease. Thus, pneumonia is seen more often in the winter months. December and January demonstrated a peak three-to five-fold greater than August.[3,4] Droplet size and transmission rate in infectiously transmissible crowded environments: in poorly ventilated or crowded environments, exposure levels rise.[18]

Furthermore, we know that lack of access to health care and maternal education status are the other risk factors for pneumonia.[19] Rural mothers do not know enough about pediatric pneumonia. Even when their children have severe pneumonia or an extremely severe illness, they do not seek adequate treatment.[20] However, our participants were residing in Istanbul around our hospital, and all of them had health insurance.

In several studies, it has also been found that not feeding breast milk increases the risk of pneumonia in small children.[5,19,21] In our study, patients and controls did not make a difference depending on breastfeeding. Low birth weight, inadequate immunization, and a previous hospitalization history are the factors that predispose to pneumonia. When we compared groups in terms of birth weights, we found that the birth weights of the pneumonia group were lower than those of the control group. Although we know that proper vaccination decreases the risk of pneumonia, regarding the groups' levels of complete immunization, there was no discernible difference. Furthermore, there was no significant difference between the two groups in terms of previous hospitalization and operation history.

It is a well-known fact that pneumococcal disease is more likely to occur in homes that are overcrowded. In our study, the number of people living in the same house was slightly more than in controls. The combination of these characteristics and the presence of cigarette smoke in the house raised the likelihood that children diagnosed with pneumonia would require hospitalization.[22] However, we did not find any difference in terms of mothers' smoking situations.

In several studies in adults, there is evidence of a relationship between Vitamin D deficiency and upper respiratory tract infections. According to a meta-analysis by Jolliffe et al.[23] of data from randomized controlled trials, taking a Vitamin D supplement has a safe and generally lower risk of infection than taking a placebo. In the epithelial cells of the respiratory tract 1, 25-OH vitamin D increases the expression of antimicrobial peptides and is thus thought to protect the lungs from infection.[24] Therefore, in the case of Vitamin D deficiency or insufficiency, there is an increase in the frequency and severity of respiratory tract infections, and overall, there are many systemic reviews.[25]

Wayse et al.[26] examined the relationship between subclinical Vitamin D deficiency and severe acute lower respiratory tract infections in children under 5 years in their study. 80 hospitalized patients and 70 healthy children were taken to the study in India. In the 132 children who were at least 4 months old and for whom data were available, 28 (21%) discontinued breastfeeding before the age of 4, and 40 (30%) discontinued breastfeeding between the ages of 4 and 6. As in our study, the duration of exclusive breastfeeding was not different in cases and controls. Wayse et al.[26] found no difference between the education of the mother and father, the number of siblings, and smoking history of the family. However, in our study, when comparing the education level of the mothers, there was a significant difference between the illiterate and the high school graduates compared to the patients and healthy ones.

In a study from Türkiye held in the same months of April and May, Vitamin D deficiency and vitamin D insufficiency were found to be 8% and 25.5%, respectively, in healthy children between 1 and 16 years of age.[17] In our study comparing patient and control groups, Vitamin D insufficiency was present in the majority of patients (68.42%). In the control group, 54.39% 25(OH)-D levels ≥30 ng/mL were found.

Today, it is known that Vitamin D deficiency is related to many diseases, such as infectious diseases, autoimmune diseases, asthma, obesity, diabetes, hypertension, cardiovascular diseases, and malignancies. However, it is debatable what the optimal serum Vitamin D levels should be in order to be protected from these diseases. In some studies, 25(OH)-D levels of >30 ng/mL are considered to be sufficient. Yoon et al.,[27] found that Vitamin D deficiency in children under the age of 2 was 29.8% when a 30 ng/mL cut-off for normal serum 25(OH)-D was used. It is currently being discussed whether vitamin D treatment should be used as adjunctive immunoregulatory therapy in cystic fibrosis.[28] Supplementation of Vitamin D activates T cells and myeloid dendritic cells, and it should be above 30 ng/mL throughout the year in healthy children and adults. Understanding the expenses associated with treating pediatric pneumonia is crucial for allocating resources and establishing priorities for child health.[29] In a similar study with preliminary evidence that Vitamin D supplementation may be a possible strategy to prevent lower respiratory tract infections, when the optimal supplement dose was increased, a relative reduction in lower respiratory tract infections was detected. Existing information that is worth further confirmation may be beyond advice.[30]

CONCLUSION

The results of this study shows that domestic crowded living conditions, low maternal education levels, low birth weight, and low serum Vitamin D levels were the important risk factors for community-acquired pneumonia during childhood. Looking at the Vitamin D levels in patients with pneumonia, if necessary, in addition to standard treatment, Vitamin D supplementation may be effective in reducing the morbidity and mortality of the disease.

Statement

Ethics Committee Approval: The Göztepe Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 14.02.2012, number: 19/C).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – NÖ, ME, BİB; Design – NÖ, ME, BİB, EA; Supervision – NÖ, ME, BİB, EA; Resource – NÖ, ME, BİB; Materials – NÖ, ME; Data Collection and/or Processing – NÖ, ME; Analysis and/or Interpretation – NÖ, ME, EA; Literature Search – NÖ, ME, EA; Writing – NÖ, ME, EA; Critical Reviews – NÖ, ME, BİB, EA.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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