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ORIGINAL ARTICLE

Vitamin D Status among Neonates with Pneumonia: Relationship to Inflammatory Markers

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Abstract

Background: An important part in calcium and phosphorus balance, bone metabolism, and bone growth is played by the steroid hormone vitamin D. Vitamin D's impact on cancer, the immune system, cardiovascular disease, and glucose homeostasis has recently been revealed. The aim of this study aimed to assess blood 25-hydroxyvitamin D concentration in newborns with pneumonia and to correlate vitamin D with serum level of procalcitonin (PCT) and C-reactive protein (CRP) as a markers of acute inflammation. **Patients and methods:** This case-control study was carried out in NICU Paediatric Department at Zagazig University Hospital, during the period from March 2022 to August 2023. This study Including 30 neonates with pneumonia in addition to 30 healthy controls. Serum vitamin D, Procalcitionin, Complete Blood Count (CBC) and C-reactive protein (CRP) levels were measured for all participants. **Results:** There was a significant lower value of Serum 25 (OH) D and vitamin D in patients compared to control group. The cut off value of vitamin D in diagnosis neonatal pneumonia was <12 (ng/ml) with sensitivity 80.0% and specificity 90.0 and total accuracy 85.0%. When comparing the weight of neonatal in pneumonia group with control group regarding the weight, it was found a significant decrease in body weight in pneumonia group less than the healthy control. **Conclusion:** Vitamin D levels is associated with higher incidence of neonatal pneumonia. Vitamin D levels were significantly related to severity of pneumonia. Blood CRP was inversely associated with vitamin D in neonates with low 25(OH)D levels.

Keywords: Vitamin D, Pneumonia, Neonates, Procalcitionin

Introduction:

Pneumonia is generally understood to be lung inflammation brought on by an infectious pathogen that triggers a reaction that causes lung tissue damage. Preterm infants are particularly vulnerable to lung infections during the neonatal period because of their immature immune systems, which are a leading cause of death **[1]**.

A critical component of bone metabolism, calcium and phosphorus homeostasis, and bone growth is played by the steroid hormone is vitamin D. The effects of vitamin D on the immune system, cancer, cardiovascular disease, and glucose homeostasis has recently come to light**[2]**.

Endocrine Society recommendations divide vitamin D status into three categories: a lack of, an abundance of, and sufficiency. These classifications

are based on the amounts of serum 25-OH vitamin D that are below 20ng/ml (50nmol/L), between 21 and 29ng/ml (52.5-72.5nmol/L), and between 30 and 100ng/ml (75-250 nmol/L), respectively. Despite the widespread acceptance of this classification, significant attempts are being made to interpret the criteria behind it because vitamin D deficiency is shown to affect the majority of the world's inhabitants**[3]**.

A vitamin D deficiency is linked to various acute and chronic diseases, including cardiovascular disease, viral diseases, autoimmune diseases, certain malignancies, abnormalities of calcium metabolism, and type 2 diabetes mellitus. Vitamin D is essential for the optimal and proper physiological function of the body's systems. The absence of vitamin D is considered a global pandemic**[2]**. Neonatal sepsis risk factors include low vitamin D levels in maternal and cord blood during pregnancy. This is explained by the immune-modulating properties of vitamin D, which can increase innate immunity and trigger inflammatory mediators**[4].** Type 1 DM, allergies, and atopic disorders have all been linked to vitamin D deficiency in children and newborns. Additionally, children with pneumonia who had rickets, a vitamin D deficient symptom, have been observed**[5]**. This study's goal was to improve the health status of newborns. To quantify the 25-hydroxyvitamin D levels in newborns with pneumonia and to analyze the associations between vitamin D and markers of acute inflammation like procalcitonin (PCT) and C-reactive protein (CRP) in the blood. This study's goal was to improve the health status of newborns. To determine the amount of 25-hydroxyvitamin D in neonates with pneumonia and to determine the relationship between vitamin D and indicators of acute inflammation such as procalcitonin (PCT) and C-reactive protein (CRP) in the blood.

Methods

After our Local Ethics Committee has approved the protocol (IRB#10443), this study was carried out in NICU Paediatric Department at Zagazig University Hospital, between March and 2022 to August 2023. It enrolled 60 children neonates, they were classified into: Group I: included 30 patient term neonates with pneumonia and Group II: included 30 apparently healthy term neonates group under control. Written informed parental consent was obtained or guardians of research participants. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The age range for inclusion was one day to 28 days. The clinical picture of pneumonia includes an acute start of symptoms and signs of respiratory distress such as tachypnea, retractions, grunting, and cyanosis in addition to auscultatory findings such reduced air entry, fine crepitations, and bronchial breath sounds. According to the WHO guidelines for the standardized interpretation of pediatric chest radiographs for pneumonia diagnosis, radiological confirmation of pneumonia was made. Excluded criteria were neonates with underlying chronic respiratory disease. Neonates had immune-compromising or Chronic medical conditions include chronic cardiac disease, neuromuscular disease, and cerebral palsy predispose individuals to severe pneumonia. neonates with various congenital abnormalities, organ failures, and congenital pneumonia.

All patients had a thorough history-taking process as well as a full clinical examination, which included a general, cardiac, abdominal, and chest exam. A thorough chest auscultation was performed in the presence of any respiratory distress symptoms, such as increased breathing rate, retractions, grunting, or cyanosis.

Each newborn taking part in the trial had three centimeters of venous blood drawn, which was split into two equal portions. The initial venous blood sample, 1 ml, was utilized to determine the CBC. The second aliquot 2ml of venous blood was left to clot, and then the serum was separated by centrifugation and stored at −20°C for detection of serum vitamin D, Pentraxin 3 and CRP levels.

Complete Blood Count (CBC), HB concentration, red cell count, white cell count, and platelet counts were all automatically conducted by the Sysmex (Kx-21N) automated hematological counter. 25(OH) Vitamin D serum level, CRP and procalcitonin serum level: was measured by immunoassay on cabas 8000 (Roche Diagnostic, Mannheim, Germany).

The most useful imaging technique for evaluating a newborn with respiratory distress is a chest X-ray.

Statistical analysis:

The Statistical Package for the Social Sciences SPSS version 20.0 was used to analyze the data. The mean and standard deviation of the information was shown. The Kolmogorov-Smirnov test was used to look at how the data were distributed. Using the independent samples t-test, the means of the two groups were compared. The ratios were analyzed using the Chi-squared test. Statistics of importance was set at $p < 0.05$ for all analyses.

Results:

Table 1; showed that there was no statistically difference between studied groups regarding to age and sex p>0.05.

Table 2; showed that there was statistically significant lower body weight in diseased group compared to healthy control group, p<0.05. But there was no statistically difference between studied groups regarding to gestational age per weeks or mode of delivery p>0.05.

Table 3; showed that there was statistically significant higher respiratory rate and heart rate body temperature in diseased group compared to healthy control group, p<0.05.

Table 4 shows; There was a significant higher value of serum 25(OH) D in mild pneumonia and a lower value in moderate pneumonia and a lower value in severe pneumonia, i.e., an inverse relationship with the severity of neonatal pneumonia.

Define that, mean hospital stay of pneumonic neonate was 7.7±1.72, ranged from (5-12) days.

Table 5 shows; There was significant inverse correlation of serum 25 (OH) D and respiratory rate/ minute, serum CRP, Procalcitonin, Pneumonia severity, duration of hospital stay p<0.05.This meaning that decrease Serum 25 (OH) D pneumonic neonate associated with increase in respiratory rate/ minute, also associated with increase serum CRP, Procalcitonin, Pneumonia severity, in addition with decrease Serum 25 (OH) D pneumonic neonate leading increase duration of hospital stay for them. Otherwise; there is no correlation of serum 25 (OH) D and other parameters p>0.05.

Table (1): Age and gender of studied groups

Variables	Neonatal pneumonia Group n.30	Healthy control Group n.30	u	p
Age per days Mean ±SD range	3.53±4.45 1-20	2.4±2.51 1-10	1.45	0.146
Gender n (%) Females Males	12(40.0) 18(60.0)	15(50.0) 15(150.0)	χ 2 0.606	0.436

u: Mann whitnney u test, χ 2 Chi square test, p >0.05 no significant

Table (2): Gestational age per weeks, mode of delivery and weight of studied groups

variables	Neonatal pneumonia Group n.30	Healthy control Group n.30	u	p
Mothers intake Vitamin D	1(3.3)	0.0	f	0.99
Mothers exposure to sun rays	1(3.3)	0.0	f	0.99
Gestational age per weeks Mean ±SD range	37.73±0.58 37-39	37.53 ± 0.73 37-39	1.17	0.246
Body Weight per (kg) Mean ±SD range	2.92±0.41 2.25-3.6	3.19±0.38 2.5-3.9	2.56	0.013*

Mode of delivery n. (%) C/S Normal vaginal delivery	25(83.3) 5(16.7)	23(76.7) 7(23.3)	0.417	0.519

u: Mann whitnney u test, f:Fisher exact test p >0.05 no significant ,* p<0.05 significant

Table (3): Vital sign of studied groups

Variables	Neonatal pneumonia Group n.30	Healthy control Group n.30	t	p
Respiratory rate/ minute Mean ±SD range	64.87±4.14 (60-72)	45±3.8 45(40-52)	19.26	0.0001*
Heart rate (beat/minute) Mean ±SD range	161.7±8.9 (148-177)	144.2±6.3 (134-156)	8.75	0.0001*
Body temperature (°C) **Mean ±SD** range	38.46±0.63 (37.5-40)	36.75±0.42 (36-37.2)	1.33	0.0001*

t: student' t test, p >0.05 no significant,* p<0.05 significant

Table (4): Comparison of serum 5 (OH) D (ng/ml) value according to severity of neonatal pneumonia (n.48).

	Pneumonia severity			KW	P
	Mild n.15	Moderate n.13	Severe n.2		
Serum 5 (OH) D (ng/ml) Mean ±SD • Median • (range)	13.07±7.24 9.1 5.4-25.6	7.63±5.46 6.9 5.1-25.6	6.37±0.07 6.37 6.32-6.42	8.96	0.011*

KW=Kruskall Wallius test of sig, *p<0.05 significant

Table (5): Correlation between serum 25 (OH) D and age, gestational age per week, clinical and laboratory finding of pneumonic neonate **(n=30):**

Variables	Serum 25 (OH) D (ng/ml)	
	(r)	p
Age per days	-0.141	0.457
Gestational age	-0.015	0.935
Weight per kg	0.004	0.984
Respiratory rate/ minute	**-.389***	**0.034**
Body temperature (°C)	-0.303	0.104
Heart rate (beat/minute)	-0.045	0.814
WBC(*10^3/ul)	-0.332	0.073
Hemoglobin (g/dl)	0.252	0.179
RBC(*10^6/ul)	0.332	0.073
TLC (*10^3/ul)	0.026	0.891
Serum CRP (mg/dl)	**-.681****	**0.0001**
Procalcitonin (ng/ml)	**-.393***	**0.031**
Pneumonia severity	**-.542***	**0.002**
Duration of hospital stay	**-.531****	**0.003**

(r) correlation coefficient insignificant p> 0.05 level (2-tailed).

Figure 1; showed that the sensitivity and specificity obtained to serum 25 (OH) D (ng/ml) value for diagnosis neonatal pneumonia serum 25 (OH) D) level <12 ng/ml had 80% sensitivity and 90% specificity, positive predictive value 88.9%, negative predictive value 81.8% and accuracy was 85%. So serum 25 (OH) D (ng/ml) a good marker for detect neonatal pneumonia, P=0.0001.

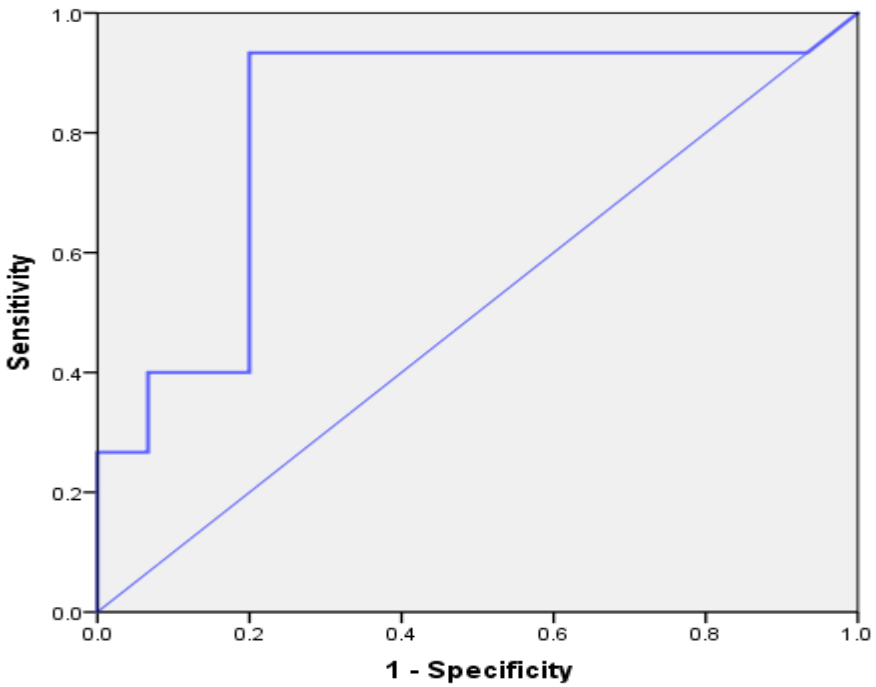

Figure (1): ROC Curve to detect the best cut-off value of serum 25 (OH) D (ng/ml) to detect severity neonatal pneumonia.

Discussion:

The findings of this investigation demonstrated that the fundamental demographic and clinical data including age (days), gender, gestational age (weeks) mother intake vitamin D or exposed to sun rays and the mode of delivery was matched without significant difference in the pneumonia and control group, this results was important to eliminate the effect of basic demographic data on the final results.

In our results when comparing the weight of neonatal in pneumonia group with control group regarding the weight, it was found a significant decrease in body weight in pneumonia group less than the healthy control.

In agreement with our results regarding low weight of pneumonia group, ***Setyarini et al*****[6]**, study the Risk Factors of Neonatal Pneumonia, they found that the low weight was characteristic for pneumonia in neonatal, According to this study, LBW was a risk factor for newborn pneumonia (p=0.000) **[6]**.

Yang also shown a connection between birth weight and neonatal pneumonia. It was discovered that newborns with low birth weight had a greater prevalence of neonatal pneumonia. Wojkowska also demonstrated that the risk of acquiring newborn pneumonia increased with birth weight**[7]**.

Babies with low birth weights have weak immune systems. Due to their weakened immune systems, LBW are more susceptible to infections, particularly pneumonia. Because the LBW respiratory control center is not ideal, anaerobic bacteria can easily grow, causing infection and eventually newborn pneumonia if oxygen levels are low**[8]**.

This study's findings demonstrated that the hemodynamic data of neonatal pneumonia group including respiratory rate, heart rate and body temperature compared to the control group, was considerably greater in the cases group.

In agreement with our results, ***Choueiry et al***, research Giant Pneumatocele Caused by Incomplete

Neonatal Pneumonia Treatment, they found an increasing in haemodynamic data including heart rate, respiratory rate and temperature in neonatal pneumonia group, heart rate was 160 beats per minute, respiration rate was 43 breaths per minute, and axillary temperature was 38.1°C **[9]**.

The findings of this investigation showed that serum 25(OH)D levels in patients were considerably lower than in the control group. In addition, sufferers' levels of sufficient vitamin D are significantly lower than those of healthy controls. regarding our results vitamin D cutoff value for diagnosis neonatal pneumonia was <12 (ng/ml) with sensitivity 80.0% and specificity 90.0 and total accuracy 85.0%.

In agreement with our results, ***El-Kassas et al*** study a case-control research called Vitamin D Status in Neonatal Pulmonary Infections looked at the vitamin's function in infant pneumonia. The results showed that individuals with pneumonia had significantly lower serum vitamin D levels than controls and people who were using mechanical ventilation than in those receiving free oxygen**[10]**.

Similarly, ***Lezhenko et al*** a significant change in 25-hydroxyvitamin D levels between healthy controls and children with community-acquired pneumonia, suggesting that young Children at risk for pneumonia have low vitamin D levels **[11].**

Dinlen et al A decreased concentration of serum 25 (OH) D was seen in neonates when compared with their moms' pneumonia to those with healthy newborns and moms**[12]**.

In the same point of view ***Mohamed and Al-Shehri,*** Lower levels of 25 (OH) D were associated with an increased incidence of acute lower respiratory tract infection (LRTI) in infancy, according to tests done on the cord blood of 206 newborns and a study of their medical records from the first two years of life**[13]**.

The findings of this research revealed a substantial connection pneumonia severity and vitamin D levels, The level of vitamin D was significantly higher compared to both mild and severe pneumonia greater in mild pneumonia, with the cutoff value of vitamin D in our results to predict the severe pneumonia was <7 ng/ml.

In agreement with our results, ***Kalembang et al***, According to the study Vitamin D Insufficiency as Risk Factor of Severe Pneumonia in Children, there is a substantial link between vitamin D deficiency and severe pneumonia in children (p=0.031). When compared to adequate Low vitamin D levels raise the chance of developing severe pneumonia by 4.71 times. This is so because vitamin D stimulates the formation of catelicidin, an antimicrobial peptide, which plays a crucial role in the innate immune response. Consequently, low vitamin D levels may increase your chance of developing pneumonia**[14]**.

Although the clinical differences between Insufficiency and a lack of vitamin D are still not clear, there are various implications of these terms for the severity of pneumonia. Severe pneumonia or sepsis can occur more frequently in people with vitamin D deficiency, but conversely, A lack of vitamin D can also lead to high mortality, bacteremia, and diseases of greater severity (such severe pneumonia) a study utilizing cut-off value <30 ng/ml reported that vitamin D insufficiency was closely associated with hypoxia and neutropenia in individuals with severe pneumonia (oxygen saturation less than 88%)**[15]**.

There are now no findings relating a lack of vitamin D to the severity of pneumonia, but numerous research have discovered a connection between the two conditions. The risk of pneumonia is 13 times higher when vitamin D deficiency is present **[16]**.

The correlation results indicated that vitamin D levels and respiratory health had a strong negative connection rate, serum CRP, proclcitonin, pneumonia severity and duration of hospital stay.

Contrarily, repeated CRP monitoring, according to **Streimish et al** is more useful for determining the length of antibiotic therapy than sepsis diagnosis **[17]**.

In agreement with our results with relation to the length of hospital stays and vitamin D levels, ***El-kassas et al*** researchers that looked at the Blood vitamin D levels and length of hospital stay were found to be negatively correlated in Vitamin D Status in Neonatal Pulmonary Infections **[10]**.

Conclusion:

Neonatal pneumonia is more common in people with decreased levels of vitamin D. Vitamin D levels were substantially linked with the severity of

pneumonia. Blood CRP and vitamin D levels were inversely associated in infants with low 25(OH)D levels.

The general population was advised to take vitamin D supplements, but this depends on the features of each nation and cannot be done consistently, especially for pregnant women, newborns, and children. In order to establish definitively if serum 25(OH) Pediatric respiratory infections are highly correlated with D concentrations; if supplementation may be useful for this age group, additional case-control clinical trials are required.

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