

## **Association between low hemoglobin level, vitamin D deficiency and acute lower respiratory tract infections in children aged 6 months to 5 years.**

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### **Abstract**

**Introduction:** Acute lower respiratory infections (ALRIs) contribute to major disease associated mortality and morbidity among children under 5 years. Research suggests that low Hemoglobin (Hb) levels and Vitamin D Deficiency are associated with ALRI. The objective of this study was to know the association of low hemoglobin levels and vitamin D Deficiency with ALRI in children aged 6 months to 5 years.

**Materials and methods:** The present study was a hospital based prospective study conducted over a period of one year, at KIMS Hospital and Research centre, Bengaluru. Children hospitalized for ALRI at KIMS Hospital, Bengaluru were included as cases; hospitalized children (6months to 5years) other than respiratory illness were included as controls.

**Results:** Among the cases, Vitamin D Deficiency, Vitamin D Insufficiency and Normal Vitamin D levels were seen in 70% (n=35), 28% (n=14), 2% (n=1) children respectively with Mean  $\pm$  SD Vitamin D levels of  $17.66 \pm 5.53$  ng/ml while controls had 16% (n=8), 24% (n=12), 60% (n=30) children respectively with a Mean  $\pm$  SD Vitamin D level of  $34.38 \pm 13.87$  ng/ml with p value <0.001. Among cases 48% (n=24) and 52% (n=26) children had Hb levels below 11g/dl and Hb above 11 g/dl respectively. While among controls 28% (n=14) and 72% (n=36) children had Hb below 11g/dl, and Hb above 11 g/dl, respectively. We found a significant correlation between Vitamin D levels and severity of ALRI with a p value of 0.03, a significant correlation between severity of ALRI and Hb levels with a p value of <0.01 and a significant correlation between Severe ALRI and combined low Hb and Vitamin D deficiency with p<0.0007.

**Conclusion:** The study shows a significant correlation between low Hb levels and Vitamin D deficiency with increased susceptibility to ALRI. Severity of ALRI is inversely related to Vitamin D levels and Hemoglobin levels and more severe with combined deficiency.

**Keywords:** ALRI, Hemoglobin levels, Vitamin D levels.

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### **Introduction**

Acute lower respiratory infections (ALRIs) contribute to major disease associated mortality and morbidity among children under 5 years. According to recent data by UNICEF around 1.73 lakh under five children in India die due to Acute Respiratory Infection (ARI), which constitutes around 15% of total Under-five deaths due to ARI [1]. In developing countries, on an average every child has five episodes of ARI/year accounting for 30%-50% of the total paediatric outpatient visits and 20%-30% of the paediatric admissions [2].

Vitamin D deficiency is considered to be the most common nutritional deficiency and is also one of the most common undiagnosed medical conditions in the world [3]. Vitamin

D has evolved into a hormone that is active throughout the body not only to regulate calcium and bone metabolism but also to reduce the risk of diseases including auto immune diseases, malignancies, cardiovascular and infectious diseases. It has been estimated that 1 billion people worldwide have Vitamin D deficiency or insufficiency [4]. Though majority of population in India lives in areas receiving ample sunlight throughout the year, Vitamin D deficiency is very common in all the age groups and both the sexes across the country [5-7]. Studies on ALRI found a significant correlation between ALRI and Vitamin D deficiency [8-11].

Anaemia prevalence in young children continues to remain over 70% in most parts of India. Hemoglobin

(Hb) level is the most reliable indicator of anaemia among all individuals. Anaemia is a major public health problem that can occur at any stage of the life cycle, but is more prevalent in pregnant women and young children having iron deficiency [12]. Approximately over 75% of children between the ages of 1-3 years are anaemic in India, and are at risk of developing various consequences of anaemia including infections [13]. Studies on ALRI found a significant correlation between ALRI and low Hemoglobin [14-17].

Since infections of the lower respiratory tract cause major morbidity and mortality among the children, identifying and treating these risk factors will have a positive effect on the wholesome growth and development of children. Our study was conducted in children aged 6 months to 5 years to know the association of low Hemoglobin levels and Vitamin D Deficiency with ALRI.

## Materials and Methods

The present study was a hospital based prospective case control study with 50 cases and 50 controls, conducted over a period of one year from October 2015 to October 2016, at KIMS Hospital and Research centre, Bengaluru. 50 hospitalized children aged between 6 months and 5 years with a clinical presentation of ALRI (Fever, cough, tachypnea/chest retractions and crackles on chest auscultation and or radiological evidence of LRTI) were included in the study as cases, 50 children (6months to 5years) hospitalized for other than respiratory illness were included as controls.. Children with Congenital malformations of chest wall, Chronic systemic illness (e.g. diabetes, immunocompromised), Protein Energy Malnutrition (Weight for age and height for age <2SD), Congenital heart disease, on Vitamin D supplementation and iron supplementation were excluded from the study.

Patients satisfying inclusion criteria were subjected to detailed history and clinical examination after obtaining Informed and written consent from the parent or guardian of the child. Weight and height were recorded for all children to assess the nutritional status. All children were evaluated by Complete Blood Picture (CBP), peripheral smear, 25-Hydroxy Vitamin D (Chemiluminescence Immunoassay). Chest x-ray was done in cases who present with signs of ALRI.

Vitamin D status in relation to [25(OH) D] level was done as follows: Vitamin D Deficiency: <20 ng/mL, Insufficiency 21-29 ng/mL, Sufficiency >30 ng/mL [18]. Based on World Health Organization Criteria, children with Hemoglobin Less than 11 g/dl were grouped under Low Hemoglobin [19]. The study subjects belonged to the same geographic area and time period thereby reducing the Vitamin D exposure differences.

The Statistical software MedCalc 14.8.1 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

## Results and Observations

### General description

The present study included 100 children Aged 6 months to 5 years. Among 50 cases, 23 of them presented with clinical picture of bronchopneumonia and 18 presented with wheeze associated ALRI, 5 presented with bronchiolitis and 4 with pneumonia. Fifty infants with no symptoms or signs of respiratory infection were recruited from the Hospital as the control group. Both the groups were age and sex matched. The mean age of infants included in the study was  $26.88 \pm 3.59$  months. Among the total number of studied infants 62 (62%) were males and 38 (38%) were females (Table1).

Amongst the study subjects present with ALRI, Vitamin D Deficiency, Vitamin D Insufficiency and Normal Vitamin D levels were seen in 70% (n=35), 28% (n=14) and 2% (n=1) children, respectively with Mean  $\pm$  SD Vitamin D levels of  $17.66 \pm 5.53$  ng/ml while controls had 16% (n=8), 24% (n=12) and 60% (n=30) children respectively with a Mean  $\pm$  SD Vitamin D level of  $34.38 \pm 13.87$  ng/ml. It was observed that control group had higher levels of Vitamin D than cases, which was statistically significant (p value<0.001) (Table 1).

In cases 48% (n=24) and 52% (n=26) children had Hb below 11 g/dl and Hb above 11 g/dl, respectively. While among controls 28% (n=14) and 72% (n=36) children had Hb below 11g/dl, and Hb above 11 g/dl, respectively. It was observed that the Mean  $\pm$  SD ( $11.98 \pm 1.70$  g/dl) of Hb levels in controls was higher than cases which had Mean  $\pm$  SD ( $10.70 \pm 1.69$  g/dl) with a significant P value of 0.002 (Table 1).

### Severity of ALRI

63.3% (n=23) of Vitamin D Deficient cases had severe respiratory findings with a Mean Vitamin D levels of  $14.40 \pm 4.63$  ng/ml while 37.7% (n=13) had mild respiratory findings with a Mean Vitamin D levels of  $20.92 \pm 4.35$  ng/ml. In the above case groups it was noted that children with severe respiratory findings had lower Vitamin D levels as compared to Vitamin D levels in children with milder symptoms which was statistically significant with a p value of 0.0001 (Table 2 and Figure 1).

We observed a significant correlation between Vitamin D levels and severity of ALRI with spearman's correlation of r being -0.3 with a p value of 0.03. There was a significant correlation between severity of ALRI and Hemoglobin levels with r value of -0.34 and a p value of <0.01.

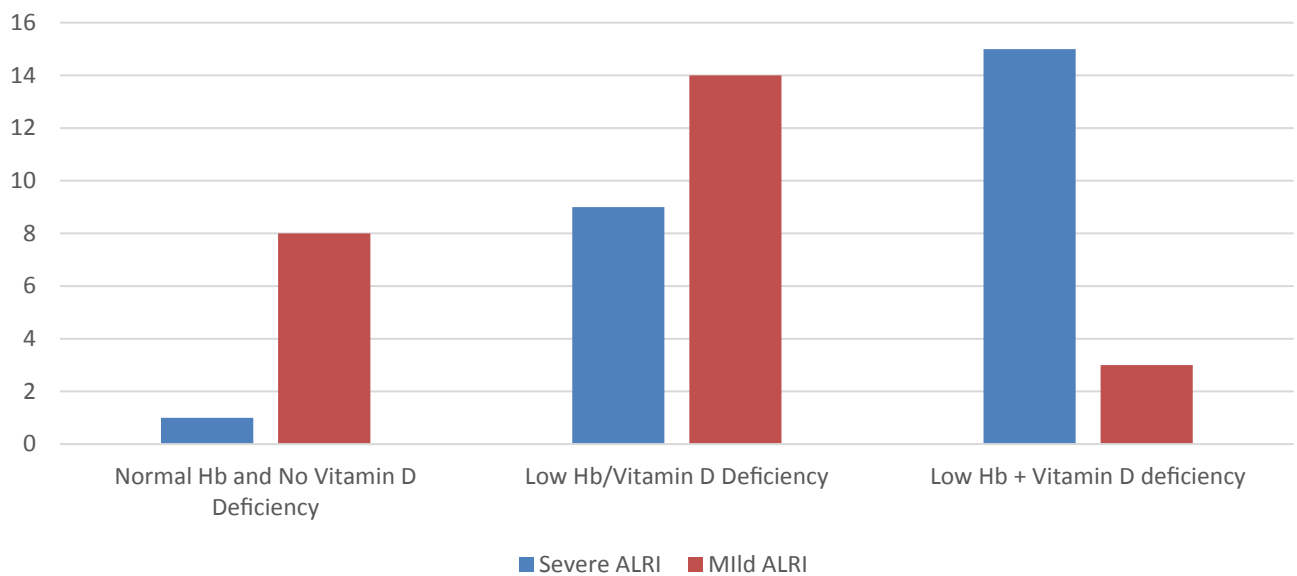
36% (n=18) of cases had both Low Hb and low Vitamin D of which 83% (n=15) had Severe ALRI, 46% (n=23) cases had either Low Hb or Vitamin D deficiency of which 39% (n=9) had severe ALRI, 18% (n=9) cases had Normal Hemoglobin and Normal Vitamin D of which 11% (n=1) had severe ALRI and a significant correlation was observed between Severe ALRI and combined low Hb and Vitamin D deficiency with p value of 0.0007 on chi square test.

**Table 1.** Descriptive statistics of cases and controls

		Cases (%)	Controls (%)
<b>Age</b>	<1 year	12	11
	1-2 years	18	19
	2-5 years	20	20
<b>Gender</b>	Female	18 (36%)	20(40%)
	Male	32 (64%)	30 (60%)
<b>ALRI</b>	Mild	25 (50%)	0 (0%)
	Severe	25 (50%)	0 (0%)
<b>Vitamin D3 levels (ng/ml)</b>	<20 ng/ml	35 (70%)	8 (16.0%)
	20-30 ng/ml	14 (28%)	12 (24.0%)
	>30 ng/ml	1 (2.0%)	30 (60.0%)
	Total	50 (100%)	50 (100.0)
	Mean ± SD	17.66 ± 5.53 ng/ml	34.37 ± 13.87 ng/ml
	P value	<0.001 (student t test)	
<b>Hemoglobin levels (g/dl)</b>	<11 g/dl	24 (48.0%)	14 (28.0%)
	>11 g/dl	26 (16.0%)	36 (52.0%)
	Total	50 (100.0%)	50 (100.0%)
	Mean ± SD	10.70 ± 1.69 g/dl	11.97 ± 1.69 g/dl
	P value	0.002 (student t test)	
<b>Severity of ALRI vs. Vitamin D3 levels</b>	r Value	-0.605	-
	p value	0.001	-
<b>Severity of ALRI vs. Hemoglobin levels</b>	r Value	-0.34	-
	p value	0.01	-

**Table 2.** Correlation between vitamin D, low hemoglobin and severity of ALRI

	Mild ALRI	Severe ALRI	P value
<b>Mean Vitamin D3 levels (ng/ml)</b>	20.92 ± 4.35	14.40 ± 4.63	0.0001
<b>Mean Hemoglobin levels (g/dl)</b>	11.31 ± 1.1	10.1 ± 1.98	0.001
<b>Normal Hb and No Vitamin D Deficiency</b>	8 (89%)	1 (11%)	0.0007
<b>Low Hb/Vitamin D Deficiency</b>	14 (61%)	9 (39%)	
<b>Low Hb+Vitamin D deficiency</b>	3 (17%)	15 (83%)	



**Figure 1:** Correlation between vitamin D, low hemoglobin and severity of ALRI

## Discussion

ALRI remains a significant health problem in India with significant morbidity and mortality. According to WHO estimates, Acute Respiratory Infection (ARI), in the form of Pneumonia remains the leading infectious cause of death among children under five, killing 2,500 children a day. Pneumonia accounted for 15 percent of all under-five deaths and killed 920,000 children in 2015. Most of its victims were less than 2 years old [20]. More than 95% of clinical Pneumonia in young children worldwide occurs in developing countries.

There is growing evidence that the effects of Vitamin D reach far beyond calcium and bone metabolism. In recent years several immune modulatory effects of Vitamin D have been described [21]. Vitamin D deficiency is a common and important nutritional deficiency in children. Clinical and subclinical Vitamin D deficiency in children has been reported to be a significant risk factor for severe acute lower respiratory tract infection [22].

Anaemia is the commonest ailment affecting human's health, socio-economic development and overall betterment of the mankind. Most common cause for anaemia is nutritional deprivation, particularly iron deficiency. According to world health organization more than half of children in the South-East Asia and African Regions (53.8% or more) are classified as having anaemia [23]. Balanced and adequate nutritional supplementation to the growing children is of immense importance for development and maturity of immunity, consequently development of resistance against the infections. So nutritional inadequacy including the iron deficiency forms an indirect risk factor for the contracting acute lower respiratory tract Infection (ALRI).

This study is an attempt to find out the correlation between the ALRI, Low hemoglobin levels and Vitamin D deficiency. In this study we included children from same geographic area and time period thereby reducing the Vitamin D exposure differences.

In the present study Cases had Lower Vitamin D levels while the Controls had higher Vitamin D levels with a significant correlation and p value of less than 0.001. A similar study by Basha et al [8] in 170 children found a significant correlation between Vitamin D Deficiency and severe pneumonia in hospitalized children below 5 years of age. Karatekin [9] and colleagues studied 25 newborns with ALRI and 15 healthy newborn control subjects in Istanbul, Turkey, and found that newborns with ALRI had significantly lower serum 25(OH)D concentrations than the newborns in control group ( $9.12 \pm 8.88$  ng/ml vs.  $16.33 \pm 13.42$  ng/ml,  $p=0.011$ ). Larkin et al. [10] in the meta-analysis of 18 studies found that VDD was associated with increased risk or severity of ALRI in 13 studies; associations were not found in 4 studies. In one study it was found that high maternal Vitamin D levels were associated with ALRI in infants.

A significant correlation was observed between Vitamin D levels and severity of ALRI with a p value of 0.019 (fisher exact test) and spearman's correlation of r being -0.3 with a p value of 0.03. Similar significant and independent (controlled for age, season and pathogen) negative correlation to pneumonia severity was seen in a study by Pletz et al. in 300 patients [24]. Similarly McNally et al. [11] studied young children with severe acute lower respiratory infection and found that significantly more children admitted to the pediatric intensive care unit with ALRI were Vitamin D deficient.

We observed a significant correlation with r value-0.34 between severity of lower respiratory infection and Hemoglobin levels with p value of 0.01. Bhaskaram et al. in a similar study of 43 children between 3-5 years found 83% with pneumonia had Hemoglobin less than 11 g/dL [14]. De-Silva et al. [15] studied 366 children in Sri Lanka and observed that Iron supplementation significantly improves iron status and reduces morbidity from URTIs in children with or without infection. Mourad et al. [16] in a study involving 200 children found that Anaemic children were two times more susceptible to lower respiratory tract infection compared to the control and Ramakrishna et al. [17] in a study of 100 children with ALRI found that Anaemic children were 5.75 times more susceptible to LRTI compared to the control group.

Significant correlation was observed between severe ALRI and combined low Hb and low Vitamin D with a p value < 0.0007. EL Sakka [25] studied 96 infants with ALRTI and observed that Vitamin D Deficiency and low Hemoglobin level were positively correlated with the severity of ALRTIs ( $r=0.798$  and  $P=0.001$ ) and ( $r=0.708$ ,  $P=0.028$ ), respectively. These findings are similar to the ones we found in this study.

## Drawbacks

Sample size is small. Further studies with large sample size are needed to affirm the correlation.

## Conclusion

ALRI causes significant mortality and morbidity in children; we found that there was a significant correlation between low Hemoglobin levels and Vitamin D deficiency with increased susceptibility to ALRI. Severity of ALRI is inversely related to Vitamin D levels and Hemoglobin levels and more severe with combined deficiency.

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