

## Original Article

# Lower level of vitamin D3 is associated with susceptibility to acute lower respiratory tract infection (ALRTI) and severity: a hospital based study in Chinese infants

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**Abstract:** Background: Acute lower respiratory tract infection (ALRTI) has been attributed to a major cause of global child mortality. Micronutrient deficiencies have been associated with susceptibility to ALRTI. Vitamin D is an immunomodulatory molecule and its deficiency is more prevalent in ALRTI children. The present hospital based investigation aimed to decipher association of vitamin D with ALRTI in Chinese infants. Methods: Total of 110 infants, diagnosed with ALRTI and their mother enrolled in the present study. Matched healthy infants belonging to similar areas were included as healthy controls. Plasma levels of 25-OH vitamin D in all cases, their mothers and controls were quantified by enzyme linked immunosorbent assay (ELISA). Results: Plasma levels of 25-OH vitamin D was significantly lower in ALRTI cases than healthy controls ( $P < 0.0001$ ). Furthermore, infants with Pneumonia displayed reduce levels of vitamin D<sub>3</sub> with reference to healthy controls and no statistical significant difference was noticed between Pneumonic infants and subjects with Bronchiolitis. A positive correlation was detected in plasma levels 25-OH vitamin D in ALRTI cases and their respective mothers ( $P < 0.0001$ ,  $r = 0.57$ ). Conclusion: Lowered plasma level of 25-OH Vitamin D is linked with susceptibility to ALRTI. Positive correlation of vitamin D<sub>3</sub> in ALRTI cases and their mothers indicated supplementation of vitamin D to pregnant women may reduce the incidence of ALRTI in Chinese children.

**Keywords:** ALRTI, vitamin D, Chinese infants, pneumonia

## Introduction

Vitamin D, a micro nutrient that human obtained from food and sunlight, essential for good health. Optimum levels of Vitamin D are needed for proper functioning of various organs system. Several studies have been demonstrated possible association of vitamin D deficiency with susceptibility to wide range of disease including diabetes [1], cardiovascular diseases [2, 3] and cancer [4]. All these observations projected vitamin D as a vital molecule in pathogenesis of human diseases. Various studies have been carried out in different population to evaluate vitamin D status in healthy individuals and revealed that vitamin D deficiencies is very common in all age group [5, 6]. Vitamin D inhibits both B cells and T cells proliferations and differentiations [7-9]. Furthermore, it has dual role in inflammation: Suppresses produc-

tion of inflammatory cytokines and enhances production of anti-inflammatory molecules [10], indicating an important role of vitamin D in infections.

Subjects with vitamin D deficiency has been associated with susceptibility to respiratory tract infections. ALRTI is one of the primary cause of child death and annually about 1.4 million of children dies globally [11]. A recent report revealed an estimation of about 15 million of children admitted to hospital with severe or very severe form of ALRTI [12]. Various studies have been carried out in different populations and shown association of serum 25-OH vitamin D deficiency with increased risk of ALRTI in children from India [13] and Turkey [14]. However, another independent study failed to showed such relationship in Canadian children and infants [15]. A recent study in

## Vitamin D and ALRTI

**Table 1.** Baseline and clinical characteristics of enrolled infants

Characteristics	Controls (n=110)	ALRTI cases (n=110)	P value; $\chi^2$ ; OR
Boys/Girls	47/63	51/59	NS <sup>#</sup>
Mean age (months) $\pm$ S.D	4.00 $\pm$ 1.95	3.60 $\pm$ 1.96	NS*
Mean birth weight (kg) $\pm$ S.D	3.43 $\pm$ 0.61	3.20 $\pm$ 0.60	0.005*
Low birth weight	6 (5.4)	14 (12.7)	NS <sup>#</sup>
Premature birth	3 (2.7)	4 (3.6)	NS <sup>#</sup>
Vitamin D status			
i. Severe deficiency (<10 ng/ml)	10 (9)	36 (33)	<0.0001; 18.58; 4.86 <sup>#</sup>
ii. Deficiency (10-20 ng/ml)	54 (49)	56 (51)	NS <sup>#</sup>
iii. Insufficient (21-30 ng/ml)	36 (33)	17 (15)	0.004; 8.97; 0.37 <sup>#</sup>
iv. Sufficient (>30 ng/ml)	10 (9)	1 (1)	0.009; 6.94; 0.09 <sup>#</sup>

Note: number (%); Data are expressed as Mean  $\pm$  standard deviation; N = total numbers of study participants; ALRTI: Acute lower respiratory tract infection; NS: Not significant. \*Mean compared by student 't' test. <sup>#</sup>distribution compared by fisher test.

Chinese children revealed higher prevalence of vitamin D deficiency [16]. However, to the best of our knowledge, no reports are available on association between vitamin D deficiency and susceptibility to ALRTI and in Chinese infants. Therefore, current study aimed to investigate relationship between plasma level of vitamin D and the susceptibility and severity of ALRTI in Chinese infants.

### Materials and methods

#### Subjects

Infants (age below 1 year), those admitted to Department of Pediatrics, Affiliated Hospital of Yan'an University, Yan'an, during 2012-2015, fulfilling case definition of ALRTI were included in the present study. Healthy infants hailing from similar areas attending the hospital for vaccination during the study period were enrolled as controls. In addition, mothers of ALRTI cases were also included in the present study to find out relationship between 25-OH vitamin D among mothers and their respective infants. Birth weight and condition of birth (pre-mature/normal) were accessed retrospectively. This study and method was agreed by Human Ethical Committee of Affiliated Hospital of Yan'an University, Yan'an. Informed consent was taken from mothers and/or parent of infants. Blood samples were collected with anticoagulant from cases, their mothers and controls, plasma were separated and stored at -80°C until quantification of Vitamin D.

#### Measurement of plasma 25-OH Vitamin D

Stored samples were thawed and measured for 25-OH vitamin D by ELISA (Sigma Aldrich).

#### Statistical analysis

For all statistical analysis Graphpad prism v6.01 (Graphpad software La Jolla California USA) was used. Mean age, birth weight in ALRTI patient and control was compared by student's "t" test. Prevalence of low birth weight, premature birth and vitamin D status (severe deficiency, deficiency, insufficiency and sufficient) in controls and cases were compared by chi square test. In addition, a multivariate logistic regression analysis was performed by taking dependent variable as infants with or without ALRTI and other variables such as sex, age, LBW, preterm delivery, vitamin D levels were considered as dependent variables. For each comparison, healthy control was taken as reference group. The mean plasma levels of 25-OH Vitamin D among case and controls and between different clinical categories was compared by "t" test and ANOVA followed by Turkey's post-test, respectively. Correlation of plasma 25-OH vitamin D between infants and their respective mother and were analysed by spearman's rank test. Statistical significance value of P was fixed lesser than 0.05.

### Results

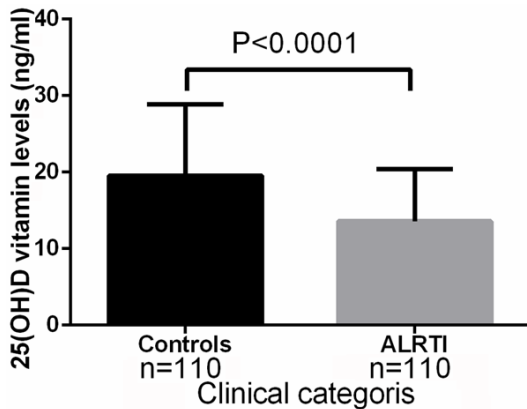
A total of 110 Chinese infants each from ALRTI cases (51 boys, 59 girls) and controls (47 boys and 63 girls) were enrolled in the current investigation. Mean  $\pm$  SD age was comparable among cases (3.6  $\pm$  1.96) and controls (4.00  $\pm$  1.95) (Table 1). Percentage of premature birth and low birth weight were comparable in ALRTI cases and controls (Table 1).

Based on 25-OH vitamin D levels subjects were categorized in to four groups. i) Sufficient (>30

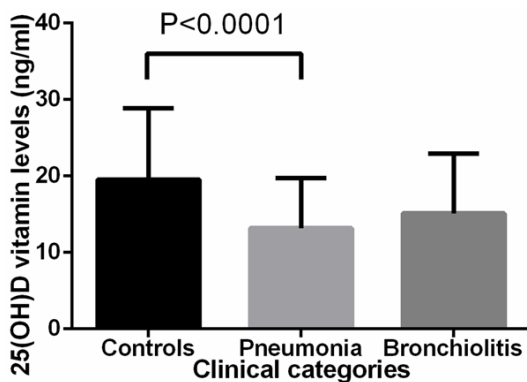
## Vitamin D and ALRTI

**Table 2.** Multivariable logistic regression analysis of determinants of ALRTI

Variables	Regression coefficient (b)	Odds ratio (OR)	95% confidence Interval (CI)		P value
			Lower	Upper	
Age	-0.07	0.92	0.79	1.07	0.32
Sex	-0.86	0.42	0.23	0.76	0.003
Birth weight	-0/60	0.54	0.30	0.97	0.03
Preterm delivery	0.72	2.05	0.29	14.37	0.46
Low birth weight	0.11	1.12	0.27	4.58	0.87
Vitamin D	-0.09	0.90	0.87	0.94	<0.0001



**Figure 1.** Plasma 25(OH) vitamin D levels in controls and patients. Plasma level of 25-OH vitamin D was quantified by ELISA. Data were expressed as Mean  $\pm$  SD.  $P < 0.05$  was statistically significant.



**Figure 2.** Plasma vitamin D levels in different clinical categories of ALRTI infants. ALRTI cases were further categorised in to Pneumonia (n=96) and Bronchiolitis (n=14). Mean plasma levels of 25-OH vitamin D of controls were compared with each clinical category. Data were expressed as Mean  $\pm$  SD.  $P < 0.05$  was statistically significant.

ng/ml), ii) Insufficient (21-30 ng/ml), iii) Deficient (10-20 ng/ml) and iv) Severe deficient

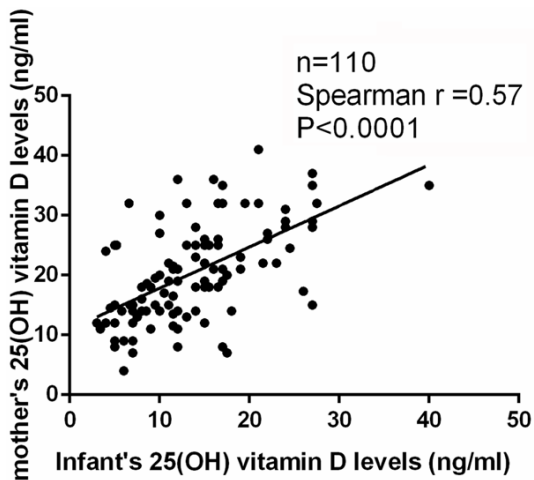
(<10 ng/ml). As depicted in **Table 1**, severe vitamin D deficiency was significantly frequent in ALRTI patients (33%) when compared to healthy controls (9%) ( $P < 0.0001$ ,  $OR = 4.86$ ,  $\chi^2 = 18.58$ ). In contrast, subjects with sufficient and insufficient vitamin D levels were more prevalent in controls compared to ALRTI cases (sufficient:  $P = 0.009$ ,  $OR = 0.09$ ,  $\chi^2 = 6.94$ ; Insuffici-

ent:  $P = 0.004$ ,  $OR = 0.37$ ,  $\chi^2 = 8.97$ ). The ALRTI cases were further categorized in to two major clinical phenotype. i) Pneumonia and ii) Bronchiolitis and distribution of various plasma vitamin D groups were compared. Patients having deficiency of 25-OH vitamin D were more frequent in pneumonia cases than bronchiolitis ( $P = 0.02$ ,  $OR = 4.51$ , 95%). Conversely, higher frequency of ALRTI patients harbouring insufficient plasma vitamin D were restricted to bronchiolitis ( $P = 0.008$ ,  $OR = 0.17$ ) (data not shown).

Since plasma 25-OH vitamin D was significantly differed between ALRTI infants and healthy controls, we further explored possible association of 25-OH vitamin D levels with severity of ALRTI. Disease severity was determined by calculating frequency of infants requiring oxygen [12]. We observed that among infected subjects, about 89% and 86% of infants at a cut-off of <10 ng/ml and 11-20 ng/ml, respectively were required oxygen for their treatment. On the other hand, only 29% of cases with 25-OH vitamin D insufficiency (21-30 ng/ml) were required oxygen indicating a significant role of vitamin D determining severity of ALRTI. Interestingly, infant with sufficient plasma vitamin D did not require oxygen support.

Further we performed a multiple logistic regression analysis to find out possible association of ALRTI with various confounding factors such as age, sex, birth weight, preterm birth, low birth weight and vitamin D levels. As shown in **Table 2**, gender, birth weight and vitamin D levels were associated with ALRTI development.

To decipher possible connection between vitamin D and ALRTI, we compared plasma 25 (OH) vitamin D levels in ALRTI infants and controls (**Figure 1**). ALRTI cases had lower levels of vitamin D in comparison to healthy infants



**Figure 3.** Correlation between plasma 25-OH vitamin D levels of mother's and infant's. Plasma levels of 25-OH vitamin D were quantified by ELISA. Correlation between mother's and infant's plasma 25-OH vitamin D were analysed by spearman rank correlation test. A P value less than 0.05 was considered as significant.

( $P < 0.0001$ ). Further, ALRTI cases were divided into Pneumonia and Bronchiolitis and plasma levels of vitamin D was compared: Pneumonia group had significantly lowered vitamin D levels when compared to healthy controls (**Figure 2**). However, among Bronchiolitis and Pneumonia/healthy infants mean vitamin D levels was comparable.

Various studies have shown positive connection of vitamin D levels between mother and infants. To reconfirm earlier observations, we investigated possible link between ALRTI cases and their mothers (**Figure 3**). Similar to earlier report, a significant positive correlation of vitamin D was observed between mothers and their infants ( $r = 0.57$ ;  $P < 0.0001$ ).

**Discussion**

In the present study, we quantified plasma vitamin  $D_3$  in Chinese infants suffering from ALRTI, their mothers and matched healthy infants. Prevalence of vitamin D deficiency was compared among healthy infants and ALRTI cases. The results of present report revealed a significant association of vitamin D deficiency with increased susceptibility to ALRTI.

25-OH vitamin  $D_3$  status has been extensively studied in various population. In Asian, a limited number of healthy individuals have suffi-

cient levels ( $>30$  ng/ml) of vitamin  $D_3$  [16-18]. A recent report in Chinese subjects showed higher frequency of vitamin D deficiency in all age group [16]. Corroborating with earlier reports, the present study also revealed higher frequency of hypovitaminosis D in our studied cohort.

The distribution of plasma vitamin  $D_3$  in ALRTI patients and healthy infants were compared by fisher exact test and observed significantly higher occurrence of vitamin D deficient in ALRTI cases than controls. This observation was in line with earlier finding in a study at Istanbul, Turkey: 76% of ALRTI infants showed vitamin D levels  $<10$  ng/ml as compared to healthy controls (40%) [14]. However, in this study, the sample size was limited (25 cases and 15 controls) in comparison to our present investigation. Frequency of higher range of plasma vitamin D levels (insufficient and sufficient) were statistically more prevalent in healthy infants compared to ALRTI cases indicating possible defensive role of Vitamin D against ALRTI.

As the prevalence of severe deficient vitamin  $D_3$  subjects was more frequent in ALRTI cases and sufficient was in healthy infant, we further interested to analyse plasma levels of vitamin  $D_3$  in ALRTI patients and healthy infants. ALRTI cases had significantly lower levels of vitamin  $D_3$  in comparison to healthy controls. This observation was similar to previous findings shown in Turkey, Bangladesh population [14, 15] and also in a very recent report [19]. Collectively, these observations suggest an imperative role of vitamin D in ALRTI.

Pneumonia and Bronchiolitis are common clinical phenotypes of ALRTI in infants [15, 20], thus we divided the ALRTI cases to Bronchiolitis and Pneumonia groups and examined the status of vitamin D in these subtypes. Although we did not observe statistical valid difference in frequencies of Pneumonic and Bronchiolitis infants showing severe vitamin D deficiency (cut-off 10 ng/ml), a significantly higher frequencies of Pneumonic infants showed vitamin D levels at a range of 11-20 ng/ml as compared to infants with Bronchiolitis indicating ALRTI cases with vitamin D deficiency predisposes to Bronchiolitis group. In contrast, frequency of 25-OH vitamin D insufficient (21-30 ng/ml) was significantly higher in Pneumonia cases than Bronchiolitis sub-type.

The scoring of severity for ALRTI depends on several signs and symptoms such as, patient's body temperature, respiratory rate, grunting, cyanosis, retractions, refusal of oral intake, and intermittent apnea [21]. Patients with apnea need oxygen for their survival and in the recent study, we considered severity of ALRTI by requirement of supplemental oxygen. We observed 89% of ALRTI cases with severe deficiency (>10 ng/ml) and 86% of cases with deficiency of vitamin D (10-20 ng/ml) required oxygen whereas only 29% of cases having vitamin D insufficient levels (20-30 ng/ml) required oxygen supply for their survival. These results indicate that vitamin D deficiency is closely associated with severity of ALRTI and corroborated with earlier observations [22, 23]. However, the mechanism how vitamin D offers protection against severity of ALRTI is not known.

Mostly, vitamin D status of mother closely linked with vitamin D levels of infants. A recent hospital based study in Turkey showed a positive association of vitamin D among infants and their mothers [19]. Furthermore, administration of vitamin D regularly to pregnant women during the last 90 days of pregnancy and the first 180 days after birth of infant, significantly reduced the chances of primary care centre visit of infant for ALRTI [24]. Here, in this report, we examined the correlation of vitamin D levels between infants with ALRTI and their mothers, and observed a positive link between them ( $P < 0.0001$ , spearman  $r = 0.57$ ). However, further study including larger sample size in different population are required to investigate whether exogenous vitamin D supplementation to mothers will reduce the frequency and severity of ALRTI in infants.

In the current study, we do not know the mechanism how sufficient levels of vitamin D minimize severity of ALRTI in Chinese infants. Possible link between vitamin D status, infections in children and immune responses has been shown in earlier reports [25]. It is also noted that vitamin D defends against microbial infections by increasing cathelicidin production and showed anti-microbial activity through toll-like receptors [26]. We believe that antimicrobial properties of vitamin D<sub>3</sub> could be responsible for minimizing ALRTI severity.

The findings of our study are important because it showed vitamin D deficit infants are susceptible to ALRTI. Earlier reports have demonstrat-

ed that appropriate quantity of the vitamin D enhances antimicrobial genes expression in human cell lines, monocytes and neutrophils [27-29]. In addition, vitamin D levels is also closely linked to pulmonary function: adults having sufficient vitamin D levels have improved lung function than those with insufficient vitamin D [30]. Thus, key inference of the current report is that increasing vitamin D levels by supplementing exogenous vitamin D in infants and their mother during pregnancy period may reduce morbidity/mortality risk of Chinese infant.

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### Disclosure of conflict of interest

None.

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## Vitamin D and ALRTI

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## Vitamin D and ALRTI

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