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Association Between Vitamin A Deficiency and Pneumonia Severity in Hospitalized Children Aged Six Months to Five Years

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Abstract

Background: Vitamin A supports respiratory immunity, but circulating retinol also falls during infection, so its relationship with pneumonia severity is uncertain.

Objective: This study aimed to examine the association between low serum vitamin A at admission and pneumonia severity in hospitalized children aged six months to five years.

Methods: In this prospective, hospital-based cross-sectional study with consecutive enrollment, 70 children admitted with pneumonia to a tertiary hospital in Kanpur, India, between December 2024 and May 2026 had serum vitamin A measured by high-performance liquid chromatography at admission. Low serum vitamin A was defined as <20 µg/dL. Severe pneumonia followed World Health Organization/Integrated Management of Childhood Illness (WHO/IMCI)-based criteria. Analyses included Fisher's exact test, prevalence and odds ratios, and exploratory Firth penalized logistic regression.

Results: Low serum vitamin A was present in 19 of 70 children (27.1%). Severe pneumonia occurred in 17 of 19 (89.5%) children with low values versus 15 of 51 (29.4%) with normal values (prevalence ratio=3.04; 95% confidence interval (CI)=1.94-4.78; odds ratio=20.4; 95% CI=4.18-99.45). The adjusted odds ratio in an exploratory model was 16.7 (95% CI=3.07-91.01). Excluding 12 children with severe acute malnutrition, all of whom also had hypoxemia, gave an odds ratio of 9.69 (95% CI=1.78-52.77).

Conclusion: Low serum vitamin A measured during acute pneumonia was strongly associated with severe pneumonia. Because retinol falls with inflammation and malnutrition was common, preexisting deficiency cannot be inferred; prospective studies with inflammatory markers and measurements before infection are needed.

Categories: Pediatrics
Keywords: malnutrition, pediatric pneumonia, serum retinol, severe pneumonia, vitamin a deficiency

Introduction

Pneumonia is one of the leading causes of morbidity, hospitalization, and mortality in children under five years of age, especially in developing countries. Despite substantial advances in childhood vaccines, antibiotics, nutrition, and health-service delivery, the burden of pneumonia among children remains disproportionately high in South Asia and sub-Saharan Africa [1]. Young children are particularly vulnerable because of their underdeveloped immune systems, smaller airways, dietary transition, and increased contact with respiratory pathogens. Host factors such as age, nutrition, socioeconomic status, immunization, and micronutrient deficiency also influence the severity and clinical outcome of childhood pneumonia [2,3].

Vitamin A is a fat-soluble micronutrient essential for normal vision, growth, cellular differentiation, epithelial integrity, and immune regulation. It is involved in maintaining the structural and functional integrity of the respiratory epithelium, an important barrier against invading microorganisms [4]. Vitamin A and its biologically active metabolite, retinoic acid, also regulate innate and adaptive immune responses through effects on lymphocyte proliferation, immunoglobulin production, cytokine signaling, and the differentiation of B and T lymphocytes [4,5]. Epithelial keratinization, impaired mucosal barrier function, decreased production of secretory immunoglobulin A, and dysregulated inflammatory responses may all accompany vitamin A deficiency and make an individual more susceptible to respiratory infections or render infection more severe [5,6].

There is a two-way association between vitamin A and infection. While pre-existing deficiency can reduce host resistance, acute infection and inflammation can decrease dietary intake, intestinal absorption, hepatic transport, and metabolic utilization, and lower circulating serum retinol concentrations [4]. Thus, a

reduction in serum retinol concentration during pneumonia could reflect chronic nutritional deficiency, the acute-phase response, or both. Vitamin A deficiency in preschool children remains a public health problem in developing countries, particularly among malnourished and poor children who lack dietary diversity and have inadequate supplementation coverage [7].

Evidence on whether low vitamin A status is associated with pneumonia severity is limited and inconsistent. An integrative review found that subclinical vitamin A deficiency exceeded 20% in every included study of children hospitalized with pneumonia, reaching 93.2% in one, but did not establish a relationship with severity [8]. Studies that examined severity directly have pointed in different directions. In a hospital-based study of *Mycoplasma pneumoniae* pneumonia, serum vitamin A was lower in severe than in non-severe disease, with deficiency in 62.5% of children aged six years or older and 85% of younger children with severe disease [9]. In a Nigerian case-control study, lower vitamin A was associated with severity in bivariate analysis, but only indoor air pollution (odds ratio (OR)=4.53) and zinc deficiency (OR=6.14) independently predicted severe pneumonia [10]. In a small Brazilian cohort of 40 children, retinol inadequacy after recovery was not associated with severity (inadequate retinol in 13.3% of severe versus 30.0% of non-severe cases; p=0.34) [11]. Retinol is also a poor marker of status during infection: in Peruvian children hospitalized with pneumonia, serum retinol was low at admission, rose during recovery, and was inversely related to C-reactive protein [12]. Supplementation trials add little clarity for treatment, as vitamin A did not reduce respiratory disease mortality (risk ratio=0.98; 95% confidence interval (CI)=0.86-1.12) or incidence (risk ratio=0.99; 95% CI=0.92-1.06) in community trials [7], and no single-nutrient treatment is currently recommended for respiratory infection in children [13].

The specific uncertainty this study addresses is therefore whether a low serum vitamin A concentration at admission identifies children with more severe pneumonia, and how much of any such association persists once malnutrition, which lowers retinol and independently worsens outcomes, is considered. Existing studies are small, vary in age range, etiology, and severity definition, and seldom report adjusted estimates. We examined this question in children hospitalized in northern India, a setting with a high burden of malnutrition. Our primary objective was to examine the association between low serum vitamin A at admission and World Health Organization (WHO)-defined severe pneumonia. Secondary, exploratory objectives were to estimate the prevalence of low serum vitamin A and to describe its relationship with oxygen saturation and its discriminatory ability for severe pneumonia. Because serum retinol was measured during acute infection, the study cannot separate preexisting vitamin A deficiency from inflammation-related reductions in circulating retinol, and results are expressed as low serum vitamin A at admission.

Materials And Methods

Study design and setting

This prospective, hospital-based cross-sectional study was conducted at Lala Lajpat Rai Hospital, affiliated with Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India, between December 1, 2024, and May 31, 2026. The hospital is a tertiary-care referral center serving urban and rural populations of Kanpur and surrounding districts. Children hospitalized with pneumonia were enrolled consecutively, and serum vitamin A concentrations were measured at admission specifically for the study, as testing was not part of routine clinical evaluation.

Study Population, Sampling, and Sample Size

Children aged 6-60 months admitted with pneumonia during the study period were assessed for eligibility. Eligible children whose parents or legally authorized guardians provided written informed consent were enrolled using non-probability consecutive sampling. Screening was performed during routine admission assessment, and a separate log of children screened, excluded, or declining participation was not maintained. A total of 70 children were enrolled, and all had complete data for the primary exposure and outcome; no participant was excluded after enrollment. The sample size was determined by the number of eligible children enrolled during the study period, and no a priori sample-size calculation was performed. The conventional formula for estimating a population proportion is:

$$[n = \frac{Z^2 p(1-p)}{d^2}]$$

where n represents the required sample size, Z is the standard normal deviate (1.96 for 95% confidence), p is the anticipated prevalence, and d is the desired absolute precision. Based on the observed prevalence of low serum vitamin A (27.1%), the achieved sample of 70 corresponds to an approximate precision of ±10.4 percentage points at the 95% confidence level. This retrospective precision estimate applies only to prevalence estimation and does not establish adequate power for the association analyses.

Inclusion and Exclusion Criteria

Children aged 6-60 months with clinically diagnosed pneumonia were eligible for inclusion. Pneumonia was

identified using WHO/IMNCI-based clinical criteria, including cough or difficulty breathing accompanied by age-specific fast breathing or chest wall indrawing [14,15]. Supporting findings included reduced chest expansion, altered percussion notes, and crepitations. Radiographic findings of lobar pneumonia, bronchopneumonia, or interstitial pneumonia were also considered where available.

Children were excluded if they had bronchiolitis, pulmonary tuberculosis, non-pulmonary infection, congenital heart disease, autoimmune disorders, inherited metabolic disorders, chronic diarrhea, congenital immunodeficiency, previous surgery, or ongoing long-term immunosuppressive therapy. These exclusions were intended to reduce diagnostic heterogeneity and the influence of conditions that could independently affect pneumonia severity, nutritional status, or vitamin A metabolism. Children whose parents or guardians did not provide consent were not enrolled.

Clinical Assessment and Pneumonia Severity Classification

Demographic, clinical, socioeconomic, nutritional, and medical history information was collected using a structured study proforma. Variables included age, sex, residence, socioeconomic status, previous respiratory infection or diarrhea, immunization history, feeding practices, and vitamin A supplementation. Socioeconomic status was assessed using the modified Kuppuswamy scale [16]. Previous vitamin A supplementation was recorded as the number of doses received under the national schedule and categorized as at least one prior dose versus none.

Clinical examination included respiratory rate, chest wall indrawing, retractions, accessory muscle use, oxygen saturation, and general danger signs. Pneumonia severity was categorized using the operational criteria adopted from the WHO/Integrated Management of Childhood Illness (IMCI) and Indian Facility-Based IMNCI frameworks [14,17-19]. Children with cough or difficulty breathing accompanied by fast breathing or chest wall indrawing, but without hypoxemia or a recorded general danger sign, were categorized as having non-severe pneumonia. The nonspecific presenting complaint of severe respiratory distress was not independently used to establish severe pneumonia.

Severe pneumonia was identified based on admission hypoxemia (SpO_2 <90%), recorded central cyanosis, or general danger signs such as inability to drink or breastfeed, persistent vomiting, convulsions, lethargy or unconsciousness, and stridor in a calm child. Severe acute malnutrition was additionally included in the operational inpatient severity categorization. Vitamin A status was not included in the severity definition. Hypoxemia and central cyanosis were conceptually distinct findings; however, the database linked the binary cyanosis variable to oxygen saturation, preventing their independent analysis. Because severe acute malnutrition was included in the operational severity classification and could also be associated with serum retinol concentration, sensitivity analyses examined its influence on the observed association.

Nutritional status was classified using WHO weight-for-length/height z-scores as severe acute malnutrition (<−3 SD), moderate acute malnutrition (−3 to <−2 SD), or adequate nutrition (⩾−2 SD) [20,21]. Mid-upper arm circumference was also categorized using thresholds of <11.5 cm and 11.5 to <12.5 cm for severe and moderate acute malnutrition, respectively. Nutritional categories based on the two methods were compared. Oxygen saturation was recorded at admission using pulse oximetry. Chest radiographs were assessed for lobar pneumonia, bronchopneumonia, or interstitial pneumonia. Hospitalization duration was obtained from the recorded length-of-stay variable.

Assessment of Serum Vitamin A

Venous blood samples were collected at admission using sterile technique, and serum was protected from light to minimize retinol degradation. Serum vitamin A, measured as all-trans-retinol, was quantified by high-performance liquid chromatography with ultraviolet detection (HPLC-UV) using the ClinRep® Complete Kit for Vitamins A and E (Order No. 22000; RECIPE Chemicals + Instruments GmbH, Munich, Germany). The manufacturer's assay procedure involves protein precipitation with an internal standard, separation using reversed-phase chromatography, and ultraviolet detection at approximately 325 nm. Quantification uses serum calibrators and quality-control materials supplied for the assay. Results were expressed in µg/dL. Serum vitamin A concentrations were categorized as normal (⩾20 µg/dL), low (10 to <20 µg/dL), or very low (<10 µg/dL). Concentrations below 20 µg/dL were combined for the primary binary comparison, while the original three-category distribution and continuous serum retinol concentrations were also analyzed.

Study outcomes

The primary exposure was admission serum vitamin A concentration, categorized as low (<20 µg/dL) or normal (⩾20 µg/dL). The primary outcome was severe pneumonia according to the operational severity criteria described above. Secondary analyses examined the prevalence of low serum vitamin A, associations with oxygen saturation and other clinical indicators, and the discriminatory ability of serum retinol concentration for identifying severe pneumonia.

Statistical Analysis

Data were compiled in Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and analyzed using Python 3.11.15 (Python Software Foundation, Beaverton, OR, USA) with NumPy 2.4.4 (NumFOCUS, Austin, TX, USA), SciPy 1.17.1 (NumFOCUS, Austin, TX, USA), pandas 3.0.2 (NumFOCUS, Austin, TX, USA), and statsmodels 0.15.0. The statistical analysis script is included in the Appendix. Categorical variables were summarized as frequencies and percentages, and continuous variables as medians and interquartile ranges following assessment of normality using the Shapiro-Wilk test. Categorical associations were examined using Fisher's exact test. The association across the original three serum vitamin A categories was assessed using the Freeman-Halton extension of Fisher's exact test. The Mann-Whitney U test was used for comparisons of continuous variables between severity groups.

The primary association between low serum vitamin A and severe pneumonia was expressed as a prevalence ratio (PR) and an OR, with corresponding 95% CIs. The PR was calculated using a log-based confidence interval and the OR using a Woolf-type CI. Spearman rank correlation was used to examine relationships between serum retinol concentration and clinical indicators. Partial rank correlations were additionally calculated for oxygen saturation after adjustment for nutritional status and pneumonia severity.

Exploratory multivariable analysis was performed using Firth penalized logistic regression to reduce small-sample bias [22]. The model included serum vitamin A status, age, sex, residence, nutritional status, and history of vitamin A supplementation. Firth regression was selected because of sparse observations, particularly the small number of children with low serum vitamin A and non-severe pneumonia. Ordinary logistic regression was also examined, and complete separation was not detected. Given the limited number of events relative to model parameters, adjusted estimates were interpreted cautiously [23].

An adjusted PR was estimated using modified Poisson regression with robust variance. Receiver operating characteristic (ROC) analysis assessed the ability of serum retinol concentration to discriminate severe from non-severe pneumonia. The area under the curve (AUC) and its 95% CI were estimated using the DeLong method [24], and an exploratory threshold was identified using the Youden index. Sensitivity analyses included excluding children with severe acute malnutrition, redefining severity without the malnutrition criterion, and varying the adjustment for nutritional status. All statistical tests were two-sided, and p-value <0.05 was considered statistically significant. Given the cross-sectional design, results were interpreted as associations rather than causal effects.

Ethical Approval and Consent

The study was approved by the Institutional Ethics Committee (Biomedical Health and Research), Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India (approval number EC/425/Nov./2024; November 4, 2024). Written informed consent was obtained from the parent or legally authorized guardian of each participating child before study-related data collection and blood sampling. Participant confidentiality was maintained throughout the study.

Results

Participant characteristics

A total of 70 children aged six months to five years who were hospitalized with pneumonia were included. The 37-60-month age group was the largest (50.0%), followed by the 13-36-month group (40.0%) and the 6-12-month group (10.0%). Male participants comprised 52.9% of participants, and urban and rural residence were equally represented (50.0% each). By the modified Kuppuswamy scale, most families belonged to lower socioeconomic strata: class III (lower middle) 42.9%, class V (lower) 32.9%, and class IV (upper lower) 24.3%. Nutritional assessment showed adequate nutrition in 47.1%, moderate acute malnutrition in 35.7%, and severe acute malnutrition in 17.1%. A previous respiratory infection or diarrhea was reported in 14.3% of children, and 68.6% had received at least one dose of vitamin A supplementation. Severe pneumonia was diagnosed in 45.7% of participants. Overall, 72.9% had normal vitamin A status, 25.7% had subclinical deficiency, and 1.4% had severe deficiency (Table *1*).

Characteristic	Category	n	Percentage
Age group (months)	6-12	7	10.0
	13-36	28	40.0
	37-60	35	50.0
Sex	Male	37	52.9
	Female	33	47.1
Residence	Rural	35	50.0
	Urban	35	50.0
Socioeconomic status (modified Kuppuswamy)	Class III (lower middle)	30	42.9
	Class IV (upper lower)	17	24.3
	Class V (lower)	23	32.9
Nutritional status	Adequate nutrition	33	47.1
	Moderate acute malnutrition	25	35.7
	Severe acute malnutrition	12	17.1
Previous respiratory infection or diarrhea	Yes	10	14.3
	No	60	85.7
Vitamin A supplementation	Received	48	68.6
	Not received	22	31.4
Pneumonia severity	Non-severe pneumonia	38	54.3
	Severe pneumonia	32	45.7
Vitamin A status	Normal (≥20 µg/dL)	51	72.9
	Subclinical deficiency (10-<20 µg/dL)	18	25.7
	Severe deficiency (<10 µg/dL)	1	1.4

TABLE 1: Baseline demographic, nutritional, and clinical characteristics of the study participants (N=70)

Values are n (%) of the 70 participants. Percentages are column percentages within each characteristic and may not total 100.0 because of rounding. No inferential test was applied to this descriptive table.

MUAC: mid-upper arm circumference; SD: standard deviation.

Among the 32 children classified as having severe pneumonia, 30 (93.8%) had admission SpO_2 <90%, including all 12 with severe acute malnutrition. Recorded objective criteria and principal danger-sign labels are summarized in Table *2*. The presenting-complaint label "severe respiratory distress" appeared in 24 records (10 severe, 14 non-severe), but did not represent a standardized severity assessment.

Severity criterion/recorded designation	n	Percentage of severe cases
Objective criteria assessed across all severe cases (not mutually exclusive)		
Oxygen saturation <90% on admission pulse oximetry (hypoxemia)	30	93.8
Severe acute malnutrition (WLZ/WHZ <−3 SD and MUAC <11.5 cm)	12	37.5
Primary danger-sign label recorded on the study proforma (mutually exclusive, summing to n=32)		
Severe acute malnutrition	12	37.5
Central cyanosis	11	34.4
Inability to drink or breastfeed	6	18.8
Lethargy	3	9.4

TABLE 2: Distribution of full-cohort objective severity criteria among children with severe pneumonia (n=32)

Objective criteria may overlap: all 12 children with severe acute malnutrition also had SpO_2 <90%. One principal danger-sign label was entered per severe case (four lower rows total n=32); additional simultaneous danger signs were not systematically available. The two non-hypoxemic severe cases had discordant recorded variables that could not be checked against original charts. The database linked binary cyanosis coding to hypoxemia, preventing independent analysis.

WLZ/WHZ: weight-for-length/height z-score; MUAC: mid-upper arm circumference; SD: standard deviation; SpO_2: peripheral oxygen saturation.

Vitamin A status and pneumonia severity

Low admission serum vitamin A (<20 µg/dL) was observed in 19 of 70 children (27.1%; 95% CI 18.1-38.5, Wilson). Severe pneumonia occurred in 15 of 51 children with normal concentrations, 16 of 18 with concentrations of 10 to <20 µg/dL, and the single child with a concentration <10 µg/dL. The three-category association was significant (Freeman-Halton exact p<0.001; Table *3*). Median retinol was 19.1 µg/dL (IQR 17.6-29.4) in severe versus 27.5 µg/dL (IQR 24.8-35.5) in non-severe pneumonia (Mann-Whitney U p=0.002).

Vitamin A status	Non-severe pneumonia, n (%)	Severe pneumonia, n (%)	Total, n (%)
Normal (≥20 µg/dL)	36 (70.6)	15 (29.4)	51 (72.9)
Subclinical deficiency (10-<20 µg/dL)	2 (11.1)	16 (88.9)	18 (25.7)
Severe deficiency (<10 µg/dL)	0 (0.0)	1 (100.0)	1 (1.4)
Total	38 (54.3)	32 (45.7)	70 (100.0)

TABLE 3: Distribution of vitamin A status according to pneumonia severity

Values are n (%). Percentages in the first two columns are row percentages within each vitamin A category; percentages in the Total column are of all 70 participants. The severe-deficiency category contained a single participant, so the chi-square approximation is unreliable and no three-way test statistic is reported; inference is based on the deficient-versus-normal comparison by Fisher's exact test in this table.

Association between vitamin A deficiency and severe pneumonia

For the binary comparison, severe pneumonia occurred in 17 of 19 (89.5%) children with low serum vitamin A and 15 of 51 (29.4%) with normal values. The PR was 3.04 (95% CI 1.94-4.78) and the OR was 20.40 (95% CI 4.18-99.45; Fisher's exact p<0.001; Table *4*). The comparison is illustrated in Figure *1*.

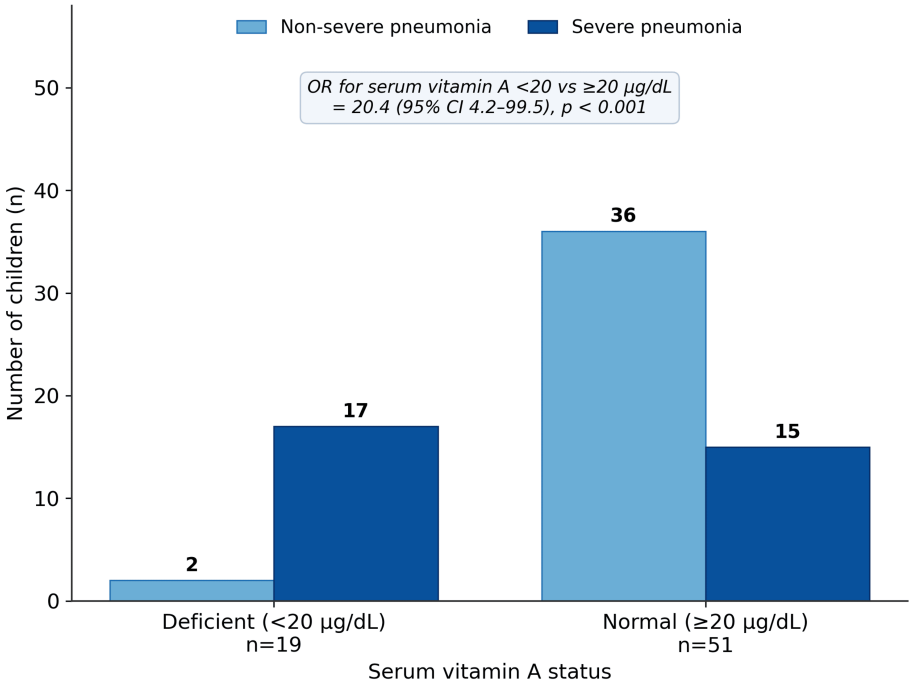


FIGURE 1: Pneumonia severity among vitamin A-deficient versus vitamin A-normal children

Deficiency defined as serum vitamin A <20 µg/dL. Severe pneumonia occurred in 17 of 19 deficient children (89.5%) versus 15 of 51 with normal status (29.4%); odds ratio=20.4 (95% CI 4.18-99.45); Fisher's exact p<0.001. As this is a cross-sectional association, a causal or temporal interpretation cannot be drawn.

Figure credits: Authors, using Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

Serum vitamin A	Severe pneumonia, n (%)	Non-severe pneumonia, n (%)	PR (95% CI)	OR (95% CI)
Low (<20 µg/dL)	17 (89.5)	2 (10.5)	3.04 (1.94-4.78)	20.40 (4.18-99.45)
Normal (≥20 µg/dL)	15 (29.4)	36 (70.6)	Reference	Reference

TABLE 4: Unadjusted association between low serum vitamin A and severe pneumonia

Values are n (%) of children within each category (row percentages). The Fisher's exact test p-value for the association is <0.001 (two-sided), used in preference to the chi-square test because of small expected cell counts.

PR: prevalence ratio with log-based (Katz) 95% CI; OR: odds ratio with Woolf-type 95% CI; CI: confidence interval.

Serum vitamin A concentration and clinical severity indicators

Serum vitamin A was positively correlated with admission oxygen saturation (Spearman r_s=0.40, p=0.001), but not with respiratory rate or duration of hospitalization (Table 5). The partial correlation with oxygen saturation was 0.25 (p=0.039) after adjustment for nutritional status and 0.15 (p=0.24) after further adjustment for pneumonia severity.

Clinical indicator	Spearman correlation coefficient (r_s)	p-Value
Oxygen saturation	0.40	0.001
Respiratory rate	-0.18	0.126
Duration of hospitalization	-0.00	0.992

TABLE 5: Correlation between serum vitamin A concentration and clinical indicators of pneumonia severity

Spearman rank correlations between serum vitamin A and the listed indicators (N=70), with two-sided p-values. Partial rank correlations for oxygen saturation were 0.25 (p=0.039) adjusting for nutritional status and 0.15 (p=0.24) additionally adjusting for pneumonia severity.

r_s: Spearman correlation coefficient.

Multivariable analysis

In exploratory Firth penalized regression adjusted for age, sex, residence, nutritional status, and prior vitamin A supplementation, low serum vitamin A was associated with severe pneumonia (adjusted OR 16.72; 95% CI 3.07-91.01; p=0.001; Table *6*). The modified Poisson adjusted PR was 3.38 (95% CI 2.07-5.51). Ordinary logistic regression converged without separation (OR 30.14; 95% CI 4.39-207.11). The Firth model had 32 outcome events for six covariates, so estimates remain exploratory.

Variable	Adjusted OR	95% CI	p-Value
Low serum vitamin A (<20 µg/dL)	16.72	3.07-91.01	0.001
Moderate/severe malnutrition	1.19	0.38-3.73	0.762
Age younger than 12 months	0.84	0.07-10.64	0.890
Male sex	1.39	0.42-4.58	0.583
Rural residence	0.38	0.12-1.25	0.111
No vitamin A supplementation	0.78	0.16-3.79	0.763

TABLE 6: Exploratory Firth penalized multivariable logistic regression of factors associated with severe pneumonia

Exploratory Firth regression with all six predictors entered simultaneously (N=70; 32 severe cases). Reference category: absence of each characteristic. Penalized Wald-type 95% CIs and p-values are reported; no complete separation was detected.

OR: odds ratio; CI: confidence interval.

Sensitivity analyses

All 12 children with severe acute malnutrition also had SpO_2 <90%; removal of malnutrition from the severity definition therefore did not change classification. Excluding these 12 children left 58 participants and 20 severe cases; seven of nine with low serum vitamin A and 13 of 49 with normal values had severe pneumonia (PR 2.93; 95% CI 1.64-5.25; OR 9.69; 95% CI 1.78-52.77; Fisher's exact p=0.006). The adjusted OR was 7.57 (95% CI 1.16-49.33; p=0.034). Additional models varying adjustment for nutritional status are shown in Table *7*.

Analysis	n	Severe pneumonia, n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Primary analysis	70	32 (45.7)	20.40 (4.18-99.45)	16.72 (3.07-91.01)
Excluding severe acute malnutrition	58	20 (34.5)	9.69 (1.78-52.77)	7.57 (1.16-49.33)
Severity redefined without the malnutrition criterion	70	32 (45.7)	20.40 (4.18-99.45)	16.72 (3.07-91.01)
Model without nutritional status	70	32 (45.7)	20.40 (4.18-99.45)	18.09 (3.32-98.50)
Nutritional status as the only covariate	70	32 (45.7)	20.40 (4.18-99.45)	14.93 (3.34-66.76)

TABLE 7: Sensitivity analyses of the association between vitamin A deficiency and severe pneumonia

Unadjusted ORs are based on 2×2 counts, with Fisher's exact test for p-values; adjusted ORs are from exploratory Firth regression.

OR: odds ratio; CI: confidence interval; MUAC: mid-upper arm circumference.

Discriminatory ability of serum vitamin A concentration

Serum vitamin A showed modest discrimination for severe pneumonia (ROC AUC 0.71; 95% CI 0.58-0.84; p=0.001; Figure *2*). The exploratory Youden threshold was 19.1 µg/dL, with sensitivity 53.1% and specificity 94.7%; in this cohort, it yielded the same classification as the 20 µg/dL cutoff.

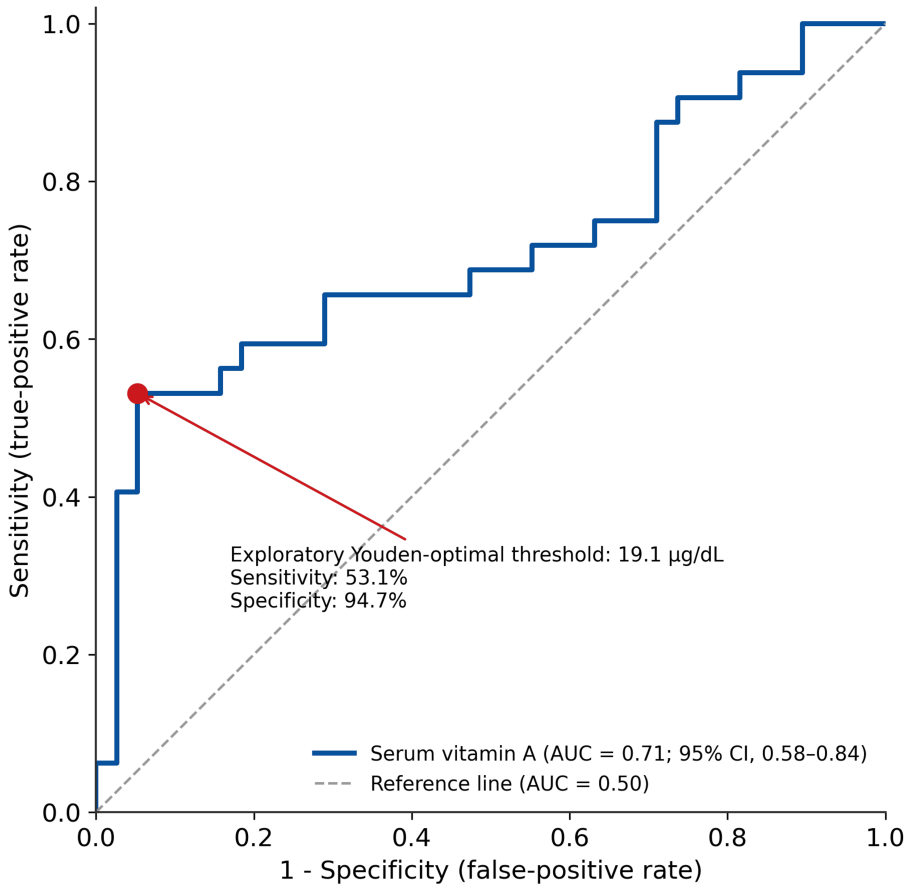


FIGURE 2: Receiver operating characteristic curve of serum vitamin A concentration for identifying severe pneumonia

The curve plots sensitivity (true-positive rate) against 1-specificity (false-positive rate), with lower serum vitamin A treated as the positive direction; the dashed line is the line of no discrimination (AUC=0.50). The red marker denotes the exploratory Youden-optimal operating point. AUC=0.71; 95% CI=0.58-0.84 (DeLong); p=0.001. Exploratory threshold=19.1 µg/dL; sensitivity=53.1%; specificity=94.7%.

AUC: area under the curve; CI: confidence interval.

Figure credits: Authors, using Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

Discussion

In this prospective cross-sectional study of 70 hospitalized children with pneumonia, low serum vitamin A at admission (<20 µg/dL) was present in 27.1% and was strongly associated with severe pneumonia (PR=3.04; unadjusted OR=20.4; adjusted OR=16.7 in an exploratory Firth model). Only two children with low values had non-severe pneumonia, so the ORs are imprecise, and the PR is the more interpretable summary. The direction is biologically plausible, since vitamin A supports respiratory epithelial integrity, mucosal immunity, and immunoglobulin production [4,5], and experimental deficiency worsens outcomes of respiratory infection [6]. It also agrees with a hospital-based study of *Mycoplasma pneumoniae* pneumonia [9] and with the high frequency of low vitamin A in children hospitalized with pneumonia [8], but not with studies in which vitamin A lost its association with severity after adjustment [10] or after recovery [11]. Our results therefore add a further association in a setting with substantial malnutrition, but do not resolve whether low vitamin A is a cause, a consequence, or a marker of severe illness.

The principal interpretive problem is that serum retinol falls during infection and with malnutrition. Retinol is bound to retinol-binding protein, a negative acute-phase reactant, so inflammation lowers circulating retinol without a change in hepatic stores, and children hospitalized with pneumonia have low retinol at admission that recovers afterwards [12]. Because C-reactive protein and similar markers were not measured, we cannot say how much of the association reflects greater inflammation in sicker children, which would produce the observed pattern without any preexisting deficiency. For this reason, we use the term low serum vitamin A and do not infer deficiency. Severe acute malnutrition added a related problem. It is a severity criterion and lowers retinol, but because all 12 affected children also had hypoxemia, the severe group was

unchanged when this criterion was removed, and the attenuation after excluding them (OR=9.69; adjusted OR=7.57) mainly reflects losing 10 of the 19 exposed children and the resulting imprecision, not definitional overlap. The association persisted and was similar with and without adjustment for nutritional status, which suggests it is not explained by malnutrition alone, though residual confounding by inflammation and diet cannot be excluded. The adjusted malnutrition estimate is not an independent effect, and the null supplementation estimate (adjusted OR=0.78) should not be read as no effect, given the few events and the uncertain ascertainment of supplementation. Cochrane evidence shows supplementation reduces mortality in at-risk children, but not respiratory-disease incidence or mortality in community trials [7], and these data cannot show whether it alters severity.

Oxygen saturation correlated with serum vitamin A (r_s=0.40), but this correlation is unadjusted; oxygen saturation is itself a severity criterion, and the association weakened to 0.25 after adjustment for nutritional status and to 0.15 (p=0.24) after further adjustment for severity, so it should not be taken as independent support. Discrimination was modest (AUC=0.71; 95% CI=0.58-0.84), with high specificity (94.7%) but low sensitivity (53.1%), and a single serum retinol measurement during acute illness is not shown here to improve on established clinical severity indicators. The findings are hypothesis-generating. They do not support testing or supplementing children on the basis of serum retinol, and evidence that vitamin A supplementation reduces the severity of pneumonia remains inconsistent [7,13].

Strengths and limitations

The study's strengths include consecutive enrollment, objective measurement of serum retinol, and the use of sensitivity analyses to examine the robustness of the observed association. However, several limitations should be acknowledged. First, this single-center cross-sectional study included a small non-probability sample without an a priori sample-size calculation, limiting generalizability and precluding causal inference. The absence of a pre-enrollment screening log also prevented assessment of exclusions and participation rates.

Second, serum retinol was measured only during acute pneumonia and may have been influenced by inflammation and malnutrition, potentially misclassifying preexisting vitamin A status [25,26]. Inflammatory biomarkers were unavailable, and repeat measurements after recovery were not performed. Although the conventional threshold of <20 µg/dL was used, an earlier exploratory analysis using <30 µg/dL was not statistically significant, indicating possible sensitivity to the selected cutoff. Accordingly, three-category and continuous analyses were also undertaken.

Third, the small number of severe pneumonia events and sparse observations among children with low retinol resulted in wide CIs and potentially unstable multivariable estimates. Pneumonia severity was predominantly determined by hypoxemia, and inconsistencies in the clinical documentation prevented complete verification of two non-hypoxemic severe cases. Severe acute malnutrition was included in the operational severity criteria, although all affected children also fulfilled the hypoxemia criterion. Furthermore, the available clinical records did not permit independent assessment of all respiratory danger signs.

Finally, some anthropometric entries required transcription corrections that could not be fully verified against source records, and detailed laboratory processing and quality-control documentation was unavailable for independent verification. These limitations warrant cautious interpretation of the findings and highlight the need for larger prospective studies incorporating standardized severity assessment, inflammatory biomarkers, and longitudinal measurements of vitamin A status.

Future directions

Whether preexisting vitamin A deficiency increases the risk of severe pneumonia requires longitudinal cohort studies with vitamin A status measured before infection, or with relative dose-response testing or inflammation-adjusted retinol, together with C-reactive protein and alpha-1-acid glycoprotein, dietary assessment, a severity definition independent of nutritional status, and sample sizes large enough for stable multivariable adjustment. Randomized trials are needed to determine whether correcting low vitamin A during pneumonia alters its course.

Conclusions

Low serum vitamin A measured during acute pneumonia was strongly associated with severe pneumonia in hospitalized children aged six months to five years, with severe pneumonia about three times as prevalent among children with low values. Because serum retinol falls with inflammation and malnutrition, and inflammatory markers were not measured, these findings do not establish preexisting vitamin A deficiency, and, as a cross-sectional exploratory analysis, they do not show causation. Longitudinal studies with measurements before infection and with inflammatory markers are needed to determine whether vitamin A deficiency predisposes to severe pneumonia.

Appendices

The statistical analysis script is available in the following link:

https://drive.google.com/file/d/14pd5aYnWQZfA_os-yRH2K_H0ejz0Pq5v/view?usp=sharing

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. GSVM Medical College issued approval EC/425/Nov/2024. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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