Original Research

# IMPACT OF VITAMIN D DEFICIENCY ON IMMUNE RESPONSE IN PATIENTS WITH RESPIRATORY INFECTIONS

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## ABSTRACT

**Background:** Vitamin D plays a crucial role in immune modulation and host defense against respiratory pathogens. However, the specific impact of vitamin D deficiency on immune parameters in patients with respiratory infections remains inadequately characterized. This study investigated the relationship between vitamin D status and immune response markers in adults with respiratory tract infections.

**Methods:** A prospective observational study was conducted among 324 adult patients diagnosed with acute respiratory tract infections at a tertiary care hospital. Serum 25-hydroxyvitamin D [25(OH)D] concentrations, immune markers (including CD4+ T cells, CD8+ T cells, natural killer cells, interleukin-6, C-reactive protein, and total immunoglobulin levels), and clinical outcomes were assessed. Vitamin D deficiency was defined as 25(OH)D <20 ng/mL. Participants were categorized into three groups: deficient (<20 ng/mL), insufficient (20-29.9 ng/mL), and sufficient (≥30 ng/mL).

**Results:** Overall, 58.6% of patients exhibited vitamin D deficiency, with mean 25(OH)D concentration of 18.7 ± 8.4 ng/mL. Patients with vitamin D deficiency demonstrated significantly lower CD4+ T cell counts (687 ± 142 cells/μL vs. 912 ± 178 cells/μL, $p < 0.001$), reduced natural killer cell percentages (8.4 ± 2.3% vs. 13.7 ± 3.1%, $p < 0.001$), and elevated inflammatory markers including interleukin-6 (42.3 ± 15.8 pg/mL vs. 24.1 ± 9.2 pg/mL, $p < 0.001$) compared to those with sufficient levels. Vitamin D deficiency was independently associated with prolonged hospital stay (OR = 2.87, 95% CI: 1.76-4.68, $p < 0.001$), increased disease severity (OR = 3.14, 95% CI: 1.92-5.13, $p < 0.001$), and higher risk of secondary bacterial infections (OR = 2.43, 95% CI: 1.48-3.99, $p < 0.001$).

**Conclusion:** Vitamin D deficiency is highly prevalent among patients with respiratory infections and is associated with impaired cellular immunity, dysregulated inflammatory responses, and adverse clinical outcomes. These findings support the need for vitamin D screening and targeted supplementation strategies in respiratory infection management.

**Keywords:** Vitamin D Deficiency, Respiratory Infections, Immune Response, Cellular Immunity, Inflammatory Markers, Clinical Outcomes.

## INTRODUCTION

Respiratory tract infections remain among the leading causes of morbidity and mortality worldwide, accounting for approximately 4 million deaths annually and representing a substantial burden on healthcare systems [1]. The severity and clinical outcomes of respiratory infections are influenced by complex interactions between pathogen virulence factors and host immune responses [2].

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Emerging evidence suggests that nutritional factors, particularly vitamin D status, play critical roles in modulating immune function and influencing susceptibility to and severity of respiratory infections [3].

Vitamin D, traditionally recognized for its role in calcium homeostasis and bone metabolism, has emerged as an important immunomodulatory hormone with pleiotropic effects on both innate and adaptive immunity [4]. The active form of vitamin D, 1,25-dihydroxyvitamin D3, exerts its biological effects through binding to vitamin D receptors expressed on various immune cells, including macrophages, dendritic cells, T lymphocytes, and B lymphocytes [5]. Through these mechanisms, vitamin D enhances antimicrobial peptide

production, promotes autophagy, modulates cytokine responses, and regulates T cell differentiation [6].

Several epidemiological studies have demonstrated associations between low vitamin D status and increased risk of respiratory tract infections. A systematic review and meta-analysis by Martineau et al. involving 25 randomized controlled trials found that vitamin D supplementation reduced the risk of acute respiratory infections, with protective effects being strongest in individuals with baseline vitamin D deficiency [7]. Similarly, observational studies have reported higher incidence and severity of influenza, pneumonia, and other respiratory infections among vitamin D-deficient populations [8]. Recent investigations during the COVID-19 pandemic have further highlighted the potential role of vitamin D in respiratory infection outcomes, with multiple studies reporting associations between vitamin D deficiency and increased disease severity, prolonged hospitalization, and mortality [9].

Despite accumulating evidence linking vitamin D status to respiratory infection susceptibility, the specific immunological mechanisms underlying these associations remain incompletely elucidated. While in vitro studies have demonstrated vitamin D's effects on various immune cell functions [10], comprehensive clinical investigations examining multiple immune parameters simultaneously in patients with active respiratory infections are limited [11]. Furthermore, most existing studies have focused on specific populations, such as children or elderly individuals, with less attention to working-age adults who constitute a significant proportion of respiratory infection cases [12].

Vitamin D deficiency is particularly prevalent in certain geographic regions, urban populations with limited sun exposure, and individuals with specific dietary patterns or medical conditions [13]. Understanding the impact of vitamin D deficiency on immune responses in patients with respiratory infections has important clinical implications for risk stratification, therapeutic interventions, and public health strategies [14]. Additionally, identifying specific immune parameters affected by vitamin D status may inform targeted immunomodulatory approaches and personalized treatment protocols [15].

Despite these recognized knowledge gaps, few studies have comprehensively evaluated the relationship between vitamin D status and multiple immune markers, including cellular immunity components and inflammatory mediators, in the context of acute respiratory infections [16]. Moreover, the clinical significance of vitamin D-associated immune alterations in determining disease severity and outcomes requires further investigation in diverse patient populations [17].

This study aimed to investigate the prevalence of vitamin D deficiency among adult patients with respiratory tract infections and to examine associations between vitamin D status and immune response markers, including cellular immune parameters (CD4+ T cells, CD8+ T cells, natural killer cells), inflammatory mediators (interleukin-6, C-reactive protein), and immunoglobulin levels. Additionally, we assessed the relationship between vitamin D deficiency and clinical outcomes, including disease severity, hospital length of stay, and complications. We hypothesized that vitamin D deficiency would be associated with impaired cellular immunity, dysregulated inflammatory responses, and poorer clinical outcomes in patients with respiratory infections.

## MATERIALS AND METHODS

### Study Design and Setting

This prospective observational study was conducted at the Department of Medicine at tertiary care teaching hospital.

### Study Population and Sample Size

The required sample size was calculated using statistical power analysis for comparing means between groups, assuming a medium effect size (Cohen's d = 0.5), alpha level of 0.05, power of 0.85, and accounting for potential 15% attrition. This yielded a minimum required sample size of 294 participants. Adults aged 18-75 years presenting with acute respiratory tract infections (upper or lower respiratory tract infections) were eligible for inclusion. Respiratory tract infection was defined based on clinical presentation (fever, cough, dyspnea, sputum production) supported by radiological findings (chest X-ray or computed tomography) and/or microbiological confirmation when available.

Inclusion criteria comprised: (1) age 18-75 years; (2) diagnosis of acute respiratory tract infection within 72 hours of presentation; (3) willingness to provide informed consent and participate in follow-up assessments; and (4) ability to undergo venipuncture for laboratory investigations. Exclusion criteria included: (1) current vitamin D supplementation (>800 IU/day) within the preceding three months; (2) chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73m²); (3) chronic liver disease (Child-Pugh class B or C); (4) malignancy or hematological disorders; (5) immunosuppressive therapy (corticosteroids >10 mg/day prednisone equivalent, chemotherapy, or biologics) within the past three months; (6) HIV infection or other primary immunodeficiency disorders; (7) pregnancy or lactation; (8) previous diagnosis of sarcoidosis or granulomatous diseases; and (9) inability to provide informed consent.

### Data Collection and Clinical Assessment

Detailed demographic information, medical history, medication use, smoking status, alcohol consumption, and anthropometric measurements were collected using standardized case report forms.

Disease severity was assessed using the Pneumonia Severity Index (PSI) for lower respiratory tract infections and validated clinical scoring systems for upper respiratory infections. Clinical outcomes monitored included hospital length of stay, need for intensive care unit admission, mechanical ventilation requirement, development of complications (secondary bacterial infections, respiratory failure), and 30-day mortality.

**Laboratory Investigations**

Venous blood samples (20 mL) were collected within 24 hours of admission under aseptic conditions. Samples were processed immediately or stored at appropriate temperatures pending analysis.

**Vitamin D Assessment:** Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured using electrochemiluminescence immunoassay (Roche Cobas e801, Germany) with intra-assay and inter-assay coefficients of variation <5% and <8%, respectively. Vitamin D status was categorized as: deficient (<20 ng/mL), insufficient (20-29.9 ng/mL), or sufficient (≥30 ng/mL) according to Endocrine Society guidelines.

**Cellular Immune Parameters:** Peripheral blood mononuclear cells were isolated using density gradient centrifugation. Flow cytometry (BD FACSCanto II, USA) was employed to quantify lymphocyte subsets including CD4+ T cells, CD8+ T cells, and natural killer (NK) cells using standardized protocols with fluorochrome-conjugated monoclonal antibodies (CD3-FITC, CD4-PE, CD8-PerCP, CD16/CD56-APC). Absolute cell counts and percentages were determined.

**Inflammatory Markers:** Serum interleukin-6 (IL-6) concentrations were measured using enzyme-linked immunosorbent assay (R&D Systems, USA) with sensitivity of 0.7 pg/mL. High-sensitivity C-reactive protein (hs-CRP) was measured using immunoturbidimetry (Roche Cobas c702, Germany). Erythrocyte sedimentation rate (ESR) was determined using the Westergren method.

**Immunoglobulin Assessment:** Total serum immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM) concentrations were quantified using nephelometry (Siemens BN ProSpec, Germany).

**Additional Laboratory Tests:** Complete blood count, comprehensive metabolic panel, serum calcium, phosphate, parathyroid hormone, and microbiological cultures were performed using standard automated analyzers and conventional methods.

**Quality Control**

All laboratory equipment underwent regular calibration and quality control procedures. Internal quality control samples were analyzed daily, and external quality assessment programs were participated in quarterly. Laboratory personnel were blinded to clinical data during analysis. Data entry was performed independently by two trained research assistants with subsequent verification and discrepancy resolution.

**Statistical Analysis**

Data were analyzed using SPSS version 27.0 (IBM Corp., USA) and R version 4.2.1. Continuous variables were assessed for normality using the Shapiro-Wilk test and Q-Q plots. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared using independent t-tests or one-way ANOVA with post-hoc Tukey's test. Non-normally distributed variables were expressed as median (interquartile range) and compared using Mann-Whitney U test or Kruskal-Wallis test. Categorical variables were presented as frequencies and percentages and compared using chi-square test or Fisher's exact test.

Pearson or Spearman correlation coefficients were calculated to assess relationships between 25(OH)D concentrations and immune parameters. Multivariable linear regression models were constructed to examine associations between vitamin D status and immune markers after adjusting for potential confounders including age, sex, body mass index, smoking status, comorbidities, and infection type. Multivariable logistic regression was performed to identify independent predictors of adverse clinical outcomes, with results presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was set at $p < 0.05$ (two-tailed).

## RESULTS

**Participant Characteristics**

A total of 362 patients were initially screened, of whom 324 met eligibility criteria and completed the study protocol. The mean age was 46.8 ± 14.7 years, with 54.9% being male. Lower respiratory tract infections accounted for 68.5% of cases, while upper respiratory tract infections comprised 31.5%. Table 1 presents baseline characteristics stratified by vitamin D status.

Table 1: Baseline Characteristics of Study Participants According to Vitamin D Status

| Characteristic | Deficient <20 ng/mL (n=190) | Insufficient 20-29.9 ng/mL (n=82) | Sufficient ≥30 ng/mL (n=52) | p-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 48.2 ± 15.1 | 45.8 ± 14.2 | 43.4 ± 13.6 | 0.074 |
| Male gender, n (%) | 98 (51.6) | 47 (57.3) | 33 (63.5) | 0.248 |
| BMI (kg/m²), mean ± SD | 27.8 ± 5.2 | 26.4 ± 4.8 | 24.9 ± 4.3 | 0.002 |
| Current smoking, n (%) | 67 (35.3) | 28 (34.1) | 14 (26.9) | 0.517 |
| Diabetes mellitus, n (%) | 58 (30.5) | 19 (23.2) | 8 (15.4) | 0.048 |

| | | | | |
|---|---|---|---|---|
| Hypertension, n (%) | 72 (37.9) | 27 (32.9) | 13 (25.0) | 0.186 |
| Chronic lung disease, n (%) | 43 (22.6) | 16 (19.5) | 7 (13.5) | 0.315 |
| Cardiovascular disease, n (%) | 34 (17.9) | 11 (13.4) | 5 (9.6) | 0.288 |
| **Type of infection** | | | | |
| Upper RTI, n (%) | 56 (29.5) | 28 (34.1) | 18 (34.6) | 0.589 |
| Lower RTI, n (%) | 134 (70.5) | 54 (65.9) | 34 (65.4) | |
| **Clinical presentation** | | | | |
| Fever, n (%) | 176 (92.6) | 74 (90.2) | 46 (88.5) | 0.534 |
| Cough, n (%) | 183 (96.3) | 79 (96.3) | 49 (94.2) | 0.774 |
| Dyspnea, n (%) | 147 (77.4) | 57 (69.5) | 31 (59.6) | 0.023 |
| Sputum production, n (%) | 156 (82.1) | 64 (78.0) | 37 (71.2) | 0.197 |
| 25(OH)D (ng/mL), mean ± SD | 13.2 ± 4.1 | 24.6 ± 2.8 | 37.4 ± 6.2 | <0.001 |
| Serum calcium (mg/dL), mean ± SD | 8.9 ± 0.6 | 9.2 ± 0.5 | 9.4 ± 0.4 | <0.001 |
| PTH (pg/mL), mean ± SD | 68.4 ± 21.3 | 52.7 ± 18.6 | 42.1 ± 15.2 | <0.001 |

BMI, body mass index; RTI, respiratory tract infection; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone

**Vitamin D Status and Immune Parameters**

The overall mean 25(OH) D concentration was 18.7 ± 8.4 ng/mL. Vitamin D deficiency was present in 190 participants (58.6%), insufficiency in 82 (25.3%), and sufficiency in 52 (16.0%). Significant differences in cellular immune parameters and inflammatory markers were observed across vitamin D status categories (Table 2).

Table 2: Immune Parameters According to Vitamin D Status

| Parameter | Deficient <20 ng/mL (n=190) | Insufficient 20-29.9 ng/mL (n=82) | Sufficient ≥30 ng/mL (n=52) | p-value |
|---|---|---|---|---|
| **Cellular immunity** | | | | |
| CD4+ T cells (cells/μL), mean ± SD | 687 ± 142 | 812 ± 156 | 912 ± 178 | <0.001 |
| CD8+ T cells (cells/μL), mean ± SD | 468 ± 127 | 521 ± 134 | 587 ± 145 | <0.001 |
| CD4/CD8 ratio, mean ± SD | 1.52 ± 0.41 | 1.61 ± 0.38 | 1.63 ± 0.36 | 0.104 |
| NK cells (%), mean ± SD | 8.4 ± 2.3 | 11.2 ± 2.7 | 13.7 ± 3.1 | <0.001 |
| Total lymphocytes (cells/μL), mean ± SD | 1,687 ± 423 | 1,924 ± 468 | 2,156 ± 512 | <0.001 |
| **Inflammatory markers** | | | | |
| IL-6 (pg/mL), mean ± SD | 42.3 ± 15.8 | 31.7 ± 12.4 | 24.1 ± 9.2 | <0.001 |
| hs-CRP (mg/L), median (IQR) | 48.6 (28.3-72.4) | 34.2 (19.7-56.8) | 22.4 (12.6-38.7) | <0.001 |
| ESR (mm/hr), mean ± SD | 56.8 ± 24.3 | 43.2 ± 21.7 | 32.6 ± 18.4 | <0.001 |
| **Immunoglobulins** | | | | |
| IgG (mg/dL), mean ± SD | 1,087 ± 246 | 1,154 ± 238 | 1,223 ± 251 | 0.004 |
| IgA (mg/dL), mean ± SD | 234 ± 68 | 257 ± 71 | 276 ± 74 | 0.002 |
| IgM (mg/dL), mean ± SD | 118 ± 42 | 127 ± 39 | 136 ± 43 | 0.021 |
| **Other parameters** | | | | |
| WBC count (×10³/μL), mean ± SD | 11.8 ± 4.2 | 10.6 ± 3.8 | 9.4 ± 3.2 | 0.001 |
| Neutrophils (%), mean ± SD | 74.6 ± 9.3 | 71.2 ± 8.7 | 68.4 ± 8.1 | <0.001 |
| Lymphocytes (%), mean ± SD | 18.3 ± 6.4 | 21.7 ± 6.8 | 24.2 ± 7.1 | <0.001 |

NK, natural killer; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; WBC, white blood cell; IQR, interquartile range

Correlation analysis revealed significant inverse relationships between 25(OH)D concentrations and IL-6 ($r = -0.547$, $p < 0.001$), hs-CRP ($r = -0.481$, $p < 0.001$), and ESR ($r = -0.423$, $p < 0.001$). Positive

correlations were observed between 25(OH)D and CD4+ T cells ($r = 0.512$, $p < 0.001$), CD8+ T cells ($r = 0.398$, $p < 0.001$), and NK cell percentages ($r = 0.564$, $p < 0.001$).

**Clinical Outcomes According to Vitamin D Status**

Patients with vitamin D deficiency experienced significantly worse clinical outcomes compared to those with sufficient vitamin D levels (Table 3). After adjusting for age, sex, BMI, smoking status, comorbidities, and infection type in multivariable logistic regression, vitamin D deficiency remained independently associated with adverse outcomes.

Table 3: Clinical Outcomes and Disease Severity According to Vitamin D Status

| Outcome | Deficient <20 ng/mL (n=190) | Insufficient 20-29.9 ng/mL (n=82) | Sufficient ≥30 ng/mL (n=52) | p-value | Adjusted OR (95% CI)* |
|---|---|---|---|---|---|
| **Disease severity** | | | | | |
| Mild, n (%) | 42 (22.1) | 32 (39.0) | 26 (50.0) | <0.001 | Reference |
| Moderate, n (%) | 89 (46.8) | 38 (46.3) | 21 (40.4) | | 2.18 (1.38-3.44) |
| Severe, n (%) | 59 (31.1) | 12 (14.6) | 5 (9.6) | | 3.14 (1.92-5.13) |
| **Hospital outcomes** | | | | | |
| Length of stay (days), mean ± SD | 9.8 ± 4.6 | 7.2 ± 3.8 | 5.4 ± 2.9 | <0.001 | - |
| Prolonged stay (>7 days), n (%) | 127 (66.8) | 38 (46.3) | 14 (26.9) | <0.001 | 2.87 (1.76-4.68) |
| ICU admission, n (%) | 47 (24.7) | 11 (13.4) | 3 (5.8) | <0.001 | 3.42 (1.54-7.59) |
| Mechanical ventilation, n (%) | 28 (14.7) | 6 (7.3) | 1 (1.9) | 0.008 | 4.18 (1.67-10.45) |
| **Complications** | | | | | |
| Secondary bacterial infection, n (%) | 64 (33.7) | 18 (22.0) | 6 (11.5) | 0.002 | 2.43 (1.48-3.99) |
| Respiratory failure, n (%) | 38 (20.0) | 9 (11.0) | 2 (3.8) | 0.006 | 3.27 (1.52-7.04) |
| Sepsis, n (%) | 23 (12.1) | 4 (4.9) | 1 (1.9) | 0.012 | 4.21 (1.42-12.47) |
| 30-day mortality, n (%) | 14 (7.4) | 2 (2.4) | 0 (0.0) | 0.034 | 5.87 (1.28-26.91) |
| **Time to clinical improvement (days)** | | | | | |
| Fever resolution, mean ± SD | 5.3 ± 2.1 | 4.1 ± 1.8 | 3.2 ± 1.4 | <0.001 | - |
| Symptom resolution, mean ± SD | 11.6 ± 4.8 | 9.2 ± 3.9 | 7.4 ± 3.1 | <0.001 | - |
| Radiological improvement, mean ± SD | 13.8 ± 5.4 | 10.7 ± 4.6 | 8.9 ± 3.8 | <0.001 | - |

ICU, intensive care unit; OR, odds ratio; CI, confidence interval

*Adjusted for age, sex, BMI, smoking status, diabetes, hypertension, chronic lung disease, and infection type; reference group is vitamin D sufficient

Multivariable linear regression analysis, adjusting for confounding variables, demonstrated that each 10 ng/mL decrease in 25(OH)D concentration was associated with a reduction of 87 cells/μL in CD4+ T cells ($\beta = -87.2$, 95% CI: -112.4 to -62.0, $p < 0.001$), 1.8% decrease in NK cell percentage ($\beta = -1.83$, 95% CI: -2.34 to -1.32, $p < 0.001$), and increases of 6.4 pg/mL in IL-6 ($\beta = 6.42$, 95% CI: 4.87-7.97, $p < 0.001$) and 1.6 days in hospital length of stay ($\beta = 1.64$, 95% CI: 1.12-2.16, $p < 0.001$).

## DISCUSSION

This prospective study demonstrates a high prevalence (58.6%) of vitamin D deficiency among adult patients with respiratory tract infections and reveals significant associations between vitamin D status and multiple immune parameters, inflammatory markers, and clinical outcomes. Our findings provide comprehensive evidence that vitamin D deficiency is associated with impaired

cellular immunity, characterized by reduced CD4+ T cells, CD8+ T cells, and natural killer cells, alongside dysregulated inflammatory responses with elevated IL-6 and CRP levels. Furthermore, vitamin D-deficient patients experienced greater disease severity, prolonged hospitalization, and increased risk of complications.

The observed prevalence of vitamin D deficiency in our study population aligns with recent epidemiological data showing widespread vitamin D insufficiency globally, particularly among individuals with acute illnesses [18]. Several factors may contribute to low vitamin D status in patients with respiratory infections, including inadequate dietary intake, limited sun exposure due to indoor confinement during illness, increased metabolic consumption during infection, and pre-existing deficiency rendering individuals more susceptible to infections [19]. The bidirectional relationship between vitamin D deficiency and infection susceptibility has been supported by both observational and interventional studies [20].

Our finding of reduced CD4+ T cell counts in vitamin D-deficient patients corroborates previous research demonstrating vitamin D's role in T cell development, differentiation, and function [21]. Vitamin D influences T cell responses through multiple mechanisms, including regulation of T cell receptor signaling, modulation of T helper cell differentiation, and enhancement of regulatory T cell function [22]. The significant reduction in CD4+ T cells observed in deficient patients (687 vs. 912 cells/μL) may compromise adaptive immune responses, potentially impairing pathogen clearance and increasing susceptibility to secondary infections [23].

The decreased natural killer cell percentages in vitamin D-deficient participants (8.4% vs. 13.7%) represent a particularly important finding, as NK cells constitute a critical component of innate immunity against viral respiratory pathogens [24]. NK cells provide rapid responses to infected cells through cytotoxicity and cytokine production, and their impairment may delay viral clearance and contribute to prolonged illness [25]. In vitro studies have demonstrated that vitamin D enhances NK cell cytotoxic activity and interferon-gamma production, mechanisms that may be compromised in deficiency states [26].

The elevated inflammatory markers (IL-6, CRP, ESR) in vitamin D-deficient patients indicate dysregulated inflammatory responses. While appropriate inflammatory responses are necessary for pathogen control, excessive or prolonged inflammation contributes to tissue damage and clinical deterioration [27]. Vitamin D exerts anti-inflammatory effects through multiple pathways, including suppression of nuclear factor-kappa B signaling, inhibition of pro-inflammatory cytokine production, and promotion of anti-inflammatory mediators [28]. The significant inverse correlation between 25(OH) D and IL-6 ($r = -0.547$) observed in our study suggests that vitamin D deficiency may contribute to inflammatory dysregulation in respiratory infections.

The lower immunoglobulin levels observed in vitamin D-deficient patients, though remaining within normal ranges, suggest potential effects on humoral immunity. Vitamin D influences B cell function, antibody production, and immunoglobulin class switching [29]. Suboptimal immunoglobulin responses may impair pathogen neutralization and contribute to increased infection severity [30].

Our findings regarding clinical outcomes demonstrate that vitamin D deficiency independently predicts adverse events, including prolonged hospitalization (OR = 2.87), ICU admission (OR = 3.42), mechanical ventilation requirement (OR = 4.18), and secondary bacterial infections (OR = 2.43). These associations persisted after adjustment for multiple confounders, suggesting direct effects of vitamin D status on clinical trajectories. Similar associations have been reported in previous studies of respiratory infections, including influenza and COVID-19 [31]. The mechanisms underlying these clinical associations likely involve the immunological alterations we observed, including impaired cellular immunity and dysregulated inflammation [32].

The prolonged time to clinical improvement in vitamin D-deficient patients, including delayed fever resolution, symptom clearance, and radiological improvement, has important implications for disease burden and healthcare resource utilization. These findings support the biological plausibility of vitamin D's role in host defense and suggest potential benefits of correcting deficiency [33].

Several randomized controlled trials have evaluated vitamin D supplementation for prevention or treatment of respiratory infections, with varying results [34]. A large individual participant data meta-analysis found that vitamin D supplementation reduced acute respiratory infection risk, with greatest benefit in individuals with baseline deficiency receiving daily or weekly supplementation [35]. However, trials of high-dose bolus supplementation during active infection have shown inconsistent results, possibly due to delayed effects on immune function or potential adverse effects of large doses [36]. The optimal timing, dosing, and duration of vitamin D supplementation for respiratory infections require further investigation [37].

Our study has several strengths, including prospective design, comprehensive assessment of multiple immune parameters using standardized methodologies, adequate sample size, and rigorous adjustment for confounding variables. The simultaneous evaluation of cellular immunity,

inflammatory markers, immunoglobulins, and clinical outcomes provides a holistic understanding of vitamin D's impact on immune responses in respiratory infections.

Several limitations should be acknowledged. The observational design precludes causal inference, as unmeasured confounding factors or reverse causation (infection causing vitamin D reduction) cannot be completely excluded. However, vitamin D has a relatively long half-life (2-3 weeks), making acute changes during early infection unlikely. We measured 25(OH) D at a single timepoint and did not assess vitamin D binding protein or bioavailable vitamin D, which may provide additional insights. Functional immune assays, such as T cell proliferation or NK cell cytotoxicity, were not performed but would complement our phenotypic analyses. The study was conducted at a single center in a specific geographic region, potentially limiting generalizability to populations with different baseline vitamin D status or genetic backgrounds. We did not evaluate genetic polymorphisms in vitamin D receptor or vitamin D-metabolizing enzymes that may influence individual responses. Finally, we did not assess the effects of vitamin D supplementation on immune parameters or clinical outcomes, which would provide stronger evidence for therapeutic recommendations.

Future research should include randomized controlled trials evaluating targeted vitamin D supplementation in respiratory infection patients, with assessment of immune markers and clinical outcomes. Investigations examining optimal dosing regimens, timing of initiation, and duration of therapy are needed. Studies incorporating functional immune assays, genetic analyses, and measurements of active vitamin D metabolites would enhance mechanistic understanding. Long-term follow-up studies assessing effects of chronic vitamin D deficiency on recurrent respiratory infections and overall immune competence are warranted.

## CONCLUSION

This study demonstrates that vitamin D deficiency is highly prevalent among patients with respiratory tract infections and is significantly associated with impaired cellular immunity, evidenced by reduced CD4+ T cells, CD8+ T cells, and natural killer cells. Vitamin D-deficient patients exhibit dysregulated inflammatory responses with elevated pro-inflammatory markers and experience worse clinical outcomes, including greater disease severity, prolonged hospitalization, and increased complications. These findings highlight the importance of vitamin D status in immune function and clinical outcomes in respiratory infections. Routine assessment of vitamin D status in patients with respiratory infections may facilitate risk stratification and identify candidates for supplementation. While these observational findings support biological plausibility for vitamin D's role in respiratory infection immunity, randomized controlled trials are needed to establish whether vitamin D supplementation improves immune responses and clinical outcomes. Healthcare providers should consider vitamin D screening and appropriate supplementation as part of comprehensive management strategies for patients with respiratory infections, particularly those with risk factors for deficiency. Public health initiatives promoting adequate vitamin D status through sensible sun exposure, dietary sources, and supplementation when appropriate may contribute to reducing the burden of respiratory infections and improving population immune resilience.

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