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Research Article

INFLUENCE OF VITAMIN D LEVELS ON IMMUNE MARKERS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Objective: This study aimed to investigate the association between serum vitamin D levels and immune markers in COPD patients compared to healthy controls, focusing on humoral and cellular immunity.

Methods: A case–control study was conducted with 75 COPD patients and 75 healthy controls. Serum Vitamin D levels were measured using enzyme-linked immunosorbent assay, and immune markers, including immunoglobulin G (IgG) levels and T-cell subsets (CD3+, CD4+, CD8+), were assessed through flow cytometry. Demographic and clinical data, such as age, gender, body mass index, and smoking history, were collected. Statistical analyses, including t-tests and Chi-square tests, were performed using Statistical Package for the Social Sciences-27 to evaluate differences and correlations between groups.

Results: COPD patients exhibited significantly lower serum Vitamin D levels (17.19±5.40 ng/mL) compared to controls (28.19±3.73 ng/mL; $p<0.001$). IgG levels were reduced in COPD patients (6.71±1.71 g/dL vs. 8.84±1.94 g/dL; $p<0.001$), indicating impaired humoral immunity. Total T-cell (CD3+) and helper T-cell (CD4+) counts were lower in COPD patients (716.53±167.31 cells/μL vs. 1024.44±219.19 cells/μL; $p<0.001$, and 659.33±169.54 cells/μL vs. 821.23±160.63 cells/μL; $p<0.001$, respectively), while cytotoxic T-cell (CD8+) counts were elevated (1268.69±229.69 cells/μL vs. 1029.61±133.93 cells/μL; $p<0.001$), leading to a reduced CD4/CD8 ratio (0.57±0.28 vs. 0.80±0.16; $p<0.001$). Strong correlations were observed between Vitamin D levels and immune markers (IgG, CD3, CD4, CD8) in COPD patients.

Conclusion: COPD patients display significant Vitamin D deficiency alongside compromised humoral and cellular immunity, marked by reduced IgG, CD3+, and CD4+ levels, elevated CD8+ levels, and a lower CD4/CD8 ratio. These findings suggest that Vitamin D deficiency may contribute to immune dysregulation in COPD, highlighting its potential as a diagnostic marker and therapeutic target for improving immune function and reducing infection risk in this population.

Keywords: Chronic obstructive pulmonary disease, Vitamin D, Immunoglobulin G, CD markers, Inflammation, CD4/CD8 ratio.

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INTRODUCTION

Vitamin D, a secosteroid hormone, has garnered substantial attention for its multifaceted roles extending beyond traditional skeletal homeostasis, notably encompassing immunomodulatory functions [1]. It exerts influence on a plethora of genes pivotal in cellular differentiation, proliferation, and overall homeostasis [2]. Vitamin D deficiency, recognized as a global health concern, has been linked to an elevated susceptibility to infections, autoimmune disorders, and chronic inflammatory conditions. The active form of Vitamin D, 1α,25-dihydroxyvitamin D, operates by binding to Vitamin D receptors, thereby modulating gene expression and influencing various metabolic pathways, including calcium and phosphate homeostasis [3]. Vitamin D's impact on the immune system is particularly noteworthy, influencing both innate and adaptive immune responses [4]. Emerging evidence suggests that Vitamin D plays a crucial role in maintaining intestinal innate immunity and gut microbiota [5]. Vitamin D deficiency is highly prevalent in patients with chronic obstructive pulmonary disease (COPD), a progressive lung disease characterized by persistent airflow limitation and frequent exacerbations. There are established studies and reviews that report Vitamin D deficiency (typically serum 25-hydroxyvitamin D <20 ng/mL or <50 nmol/L) affects a substantial proportion of COPD patients, with prevalence often ranging from 60% to 90%, varying by population, disease severity, geography, and definition used. In severe COPD (GOLD stages III–IV), rates can reach 60–77% or higher, with one study showing deficiency in 77% of patients with GOLD stage 4. Overall estimates in COPD cohorts frequently cite 60–90% prevalence, compared to lower rates in healthy controls or general populations. This high prevalence is concerning because Vitamin D deficiency is strongly associated with increased risk of recurrent respiratory infections and acute exacerbations of COPD [6].

The intricate interplay between Vitamin D and the immune system has spurred considerable research, revealing its potential to modulate immune cell function and cytokine production. Vitamin D's influence on innate immunity involves the activation of Toll-like receptors in monocytes, culminating in the induction of antimicrobial peptides such as cathelicidins, fortifying the body's defense against invading pathogens [7]. Furthermore, Vitamin D regulates intestinal barrier integrity, controlling innate and adaptive immunity in the gut [8]. In adaptive immunity, Vitamin D modulates the differentiation and function of T lymphocytes, suppressing the development of Th17 cells, which are implicated in autoimmune pathogenesis, and promoting the generation of regulatory T cells, crucial for immune tolerance and the prevention of autoimmunity. Moreover, Vitamin D plays a pivotal role in maintaining calcium homeostasis, immunology, and cell differentiation [9]. The Vitamin A and Vitamin D receptors, expressed

by the host but not the microbiota, mediate the regulation of the intestinal epithelium and mucosal immune cells, which underlie the effects of these nutrients on the microbiota [10]. Micronutrients such as Vitamins D and A have been shown to affect immune function and inflammation through different mechanisms [11]. Nutritional status significantly influences immune system efficiency; undernutrition, stemming from inadequate micronutrient consumption, can impair innate immune responses, although the impact varies across illnesses. Vitamin D supports immune function by enhancing the production of antimicrobial peptides, modulating inflammation, and aiding innate immunity. Deficiency impairs these defenses, heightening susceptibility to viral/bacterial triggers of exacerbations [12-14].

METHODS

To investigate the association of Vitamin D levels with immune markers in healthy individuals and COPD patients, we employed a case–control study design. Study participants were segregated into two groups: one is healthy controls, 75 healthy individuals without any COPD problems or any other health issues, and the second one is the COPD group: 75 COPD patients 1st time diagnosed with abnormal COPD, all the stages of GOLD, without any other comorbidities other than COPD were recruited based on their pulmonary function test results. Detailed demographic and clinical data were collected from all participants, including age, gender, body mass index, smoking history, and medication use. Serum Vitamin D was estimated with commercially available "25(OH) Vitamin-D Enzyme-linked immunosorbent assay kit (Cat. No. ab213966, Abcam, Waltham, MA 02453, USA," analytical sensitivity 1.98 ng/ml, detection range of 0.5–1010 ng/mL) according to the manufacturer's protocol. Stratification of Vitamin-D levels into deficient (levels <20 ng/mL), insufficient (between 21 and 29.9 ng/mL), and sufficient (values >30 ng/mL) was considered [15] to compare Vitamin-D status in COPD. Peripheral blood samples will be collected to assess various immune markers, including immunoglobulin G (IgG), T-cell subsets. For each sample, 20 µL CD3/CD4/CD8/CD45 four-color antibody cocktail (CD3-FITC fluorescent-labeled antibodies, CD8-PE fluorescent-labeled antibodies, CD4-PreCP, and CD4-APC fluorescent-labeled antibodies) was added to 100 µL whole blood, vortexed gently, and incubated in the dark at room temperature for 15 min. Next, 2 mL FACS Lysing Solution was added, mixed, and incubated in the dark at room temperature for 10 min to lyse erythrocytes. Samples were centrifuged (1000 rpm, 5 min), washed, resuspended in 500 µL PBS, and incubated for 5 min, then analyzed using Becton–Dickinson FACS Calibur flow cytometer with BD Biosciences version 10.8 software. MultiSET software quantified total T lymphocytes, absolute $CD4^+$and $CD3^+$, $CD8^+$ T-cell counts, and their percentages among lymphocytes and $CD3^+$ cells. Healthy adult reference ranges from standardized flow cytometry ($CD3^+$: 51.3–83.5%, $CD4^+$: 24.4–54.2%, $CD8^+$: 12.8–40.2%) benchmark alterations in Vitamin D-deficient COPD patients [16] (CD4+, CD8+, regulatory T cells). Statistical analyses using Statistical Package for the Social Sciences-27 were performed to determine the correlation between Vitamin D levels and immune markers in both healthy individuals and COPD patients using the Pearson correlation test. The normality of data distribution was assessed using Shapiro–Wilk test to validate the use of parametric tests. Differences between the two groups were analyzed using t-tests for continuous variables and Chi-square tests for categorical variables.

RESULTS

Tables 1 and 2, Figs. 1-5.

DISCUSSION

The mean age of participants in the COPD group was significantly higher (44.83±9.42 years) compared to the control group (41.89±7.5 years), indicating a modest age difference between groups (t [148]=3.197, p=0.017) (Fig. 1 and Table 1). Age and Vitamin D levels show a negative correlation [17]. This aligns with previous research

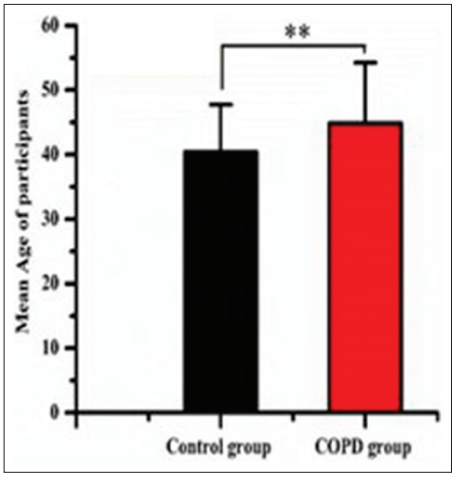

Fig. 1: The mean age of participants in the control and chronic obstructive pulmonary disease groups. Data are presented as mean±standard deviation. **p<0.01 versus control group (independent samples t-test)

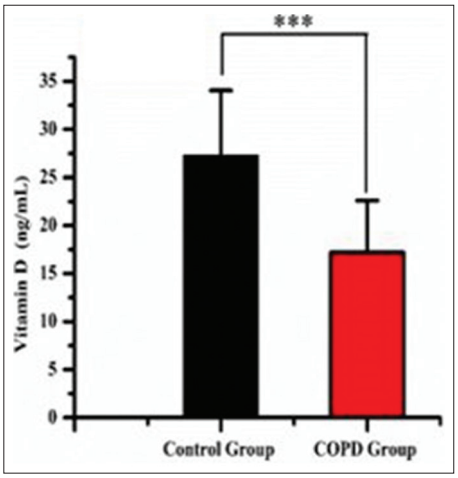

Fig. 2: Serum Vitamin D levels in control and chronic obstructive pulmonary disease groups. Data are presented as mean±standard deviation. ***p<0.001 versus control group (independent samples t-test)

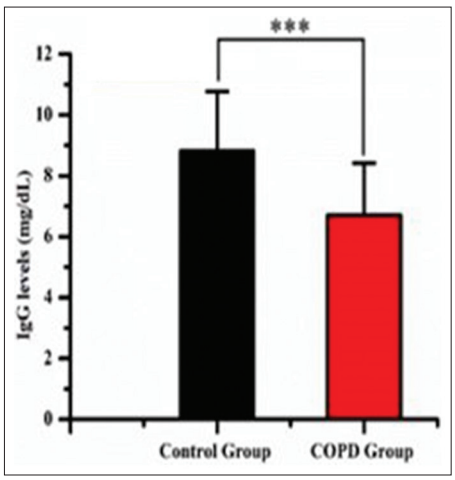

Fig. 3: Immunoglobulin G levels of participants in the control and chronic obstructive pulmonary disease groups. Data are presented as mean±standard deviation. ***p<0.001 versus control group (independent samples t-test)

Table 1: Comparison of demographic and immunological parameters between the control and COPD groups

Parameter	Control group (n=75) (Mean±SD)	COPD group (n=75) (Mean±SD)	t-value (df=148)	p-value
Age (years)	41.89±7.5	44.83±9.42	3.197	0.017
Vitamin D (ng/mL)	28.19±3.73	17.19±5.40	9.916	<0.001
PFT (FEV1%)	84.43±3.73	53.52±16.90	9.64	<0.001
IgG (g/dL)	8.84±1.94	6.71±1.71	7.035	<0.001
CD3 (cells/μL)	1024.44±219.19	716.53±167.31	9.62	<0.001
CD4 (cells/μL)	821.23±160.63	659.33±169.54	5.794	<0.001
CD8 (cells/μL)	1029.61±133.93	1268.69±229.69	7.916	<0.001
CD4/CD8 ratio	0.80±0.16	0.57±0.28	6.334	<0.001

Group comparisons were made using an independent samples t-test. SD: Standard deviation, df: Degree of freedom, PFT: Pulmonary function test (Forced Expiratory Volume1%), IgG: Immunoglobulin G; CD: Cluster of differentiation, COPD: Chronic obstructive pulmonary disease

Table 2: Assessment of Vitamin D and immunological parameters correlation within the COPD patients

Correlations								
Parameters	**Age (COPD)**	**Gender (COPD)**	**Vitamin D (COPD)**	**Ig G (COPD)**	**CD3 (COPD)**	**CD4 (COPD)**	**CD8 (COPD)**	**CD4/CD8 ratio (COPD)**
Age (COPD)								
Pearson correlation	1	0.058	−0.805**	−0.738**	−0.623**	−0.599**	0.731**	−0.682**
Sig. (2-tailed)		0.623	0.000	0.000	0.000	0.000	0.000	0.000
n	75	75	75	75	75	75	75	75
Gender (COPD)								
Pearson correlation	0.058	1	−0.123	−0.053	−0.075	−0.106	0.060	−0.125
Sig. (2-tailed)	0.623		0.293	0.650	0.523	0.365	0.608	0.287
n	75	75	75	75	75	75	75	75
Vitamin D (COPD)								
Pearson correlation	−0.805**	−0.123	1	0.904**	0.839**	0.815**	−0.877**	0.851**
Sig. (2-tailed)	0.000	0.293		0.000	0.000	0.000	0.000	0.000
n	75	75	75	75	75	75	75	75
IgG (COPD)								
Pearson correlation	−0.738**	−0.053	0.904**	1	0.914**	0.903**	−0.943**	0.957**
Sig. (2-tailed)	0.000	0.650	0.000		0.000	0.000	0.000	0.000
n	75	75	75	75	75	75	75	75
CD3 (COPD)								
Pearson correlation	−0.623**	−0.075	0.839**	0.914**	1	0.989**	−0.883**	0.930**
Sig. (2-tailed)	0.000	0.523	0.000	0.000		0.000	0.000	0.000
n	75	75	75	75	75	75	75	75
CD4 (COPD)								
Pearson correlation	−0.599**	−0.106	0.815**	0.903**	0.989**	1	−0.881**	0.935**
Sig. (2-tailed)	0.000	0.365	0.000	0.000	0.000		0.000	0.000
n	75	75	75	75	75	75	75	75
CD8 (COPD)								
Pearson correlation	0.731**	0.060	−0.877**	−0.943**	−0.883**	−0.881**	1	−0.918**
Sig. (2-tailed)	0.000	0.608	0.000	0.000	0.000	0.000		0.000
n	75	75	75	75	75	75	75	75
CD4/CD8 ratio (COPD)								
Pearson correlation	−0.682**	−0.125	0.851**	0.957**	0.930**	0.935**	−0.918**	1
Sig. (2-tailed)	0.000	0.287	0.000	0.000	0.000	0.000	0.000	
n	75	75	75	75	75	75	75	75

**Correlation is significant at the 0.01 level (2-tailed). *p<0.05, **p<0.01, ***p<0.001. IgG: Immunoglobulin G, COPD: Chronic obstructive pulmonary disease

highlighting an increased prevalence of Vitamin D deficiency in older populations [18]. This observation underscores the importance of considering age as a confounding factor in studies investigating Vitamin D status, particularly in conditions such as COPD, where older demographics are more commonly affected. There is a strong association between age in females and Vitamin D levels. This trend is consistent with existing literature suggesting that advancing age often correlates with reduced cutaneous Vitamin D synthesis and altered metabolic activation, thereby contributing to lower circulating 25-hydroxyvitamin D concentrations [19]. Furthermore, lower Vitamin D uptake has been noted among COPD patients, particularly women, which may further exacerbate their condition and impact immune responses [20].

Serum Vitamin D levels were significantly lower in the COPD group (17.19±5.40 ng/mL) compared to the control group (28.19±3.73 ng/mL), suggesting a potential role of vitamin D deficiency in COPD pathogenesis and progression ($t[148]=9.916$, $p<0.001$) (Fig. 2 and Table 1). This finding corroborates previous studies that have identified a higher prevalence of hypovitaminosis D in patients with chronic respiratory diseases, potentially influencing disease severity and immune dysregulation [21]. Vitamin D supplementation has been shown to reduce disease activity in autoimmune conditions such as systemic lupus erythematosus, underscoring its therapeutic potential in modulating immune responses [22]. The systemic inflammation characteristic of COPD, evidenced by elevated C-reactive protein and interleukin levels, may also contribute to Vitamin D malabsorption or increased catabolism, creating a cyclical relationship between

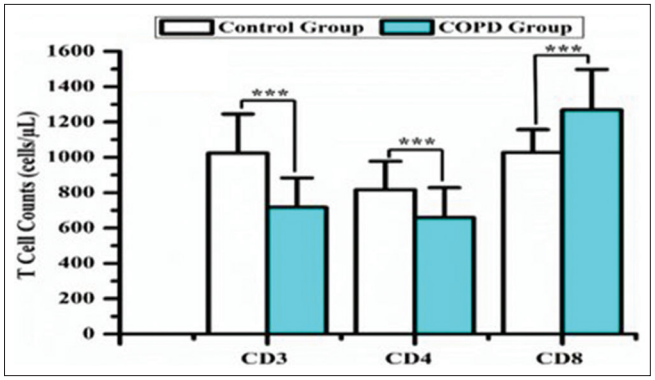

Fig. 4: T-cell counts of participants in the control and chronic obstructive pulmonary disease groups. Data are presented as mean±standard deviation. ***p<0.001 versus control group (independent samples t-test)

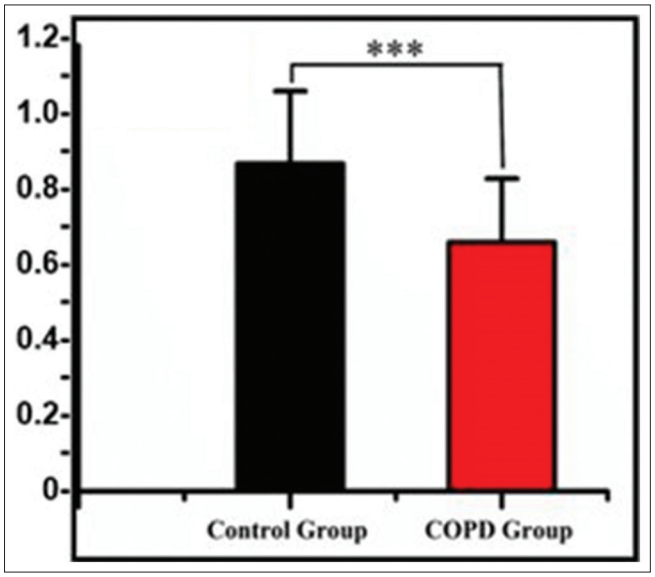

Fig. 5: CD4/CD8 ratio of participants in the control and chronic obstructive pulmonary disease groups. Data are presented as mean±standard deviation. ***p<0.001 versus control group (independent samples t-test)

inflammation and Vitamin D deficiency [23]. The observed negative correlation between age and Vitamin D levels aligns with prior findings, reinforcing the notion that Vitamin D deficiency is more prevalent in older populations, which is particularly relevant in conditions like COPD [24]. These findings reinforce the hypothesis that optimal Vitamin D levels are crucial for maintaining robust immune function, especially in vulnerable populations such as those with COPD. This is particularly pertinent given the higher susceptibility of individuals with COPD to respiratory infections, where Vitamin D's immunomodulatory roles, including the induction of antimicrobial peptides and regulation of inflammatory responses, could offer significant protective effects [25].

Serum IgG levels were markedly decreased in the COPD group (6.71±1.71g/dL) compared to the control group (8.84±1.94 g/dL), indicating impaired humoral immunity in COPD patients (t[148]=7.035, p<0.001) (Fig. 3 and Table 1). This reduction in IgG antibodies, which are critical for long-term immunity and pathogen neutralization, suggests a compromised ability to mount effective immune responses against common respiratory pathogens, a vulnerability further compounded by the chronic inflammatory state prevalent in COPD [26]. This immunodeficiency may explain, in part, the increased susceptibility of COPD patients to recurrent respiratory infections and exacerbations, which are a hallmark of disease progression. This observation is consistent with the established literature indicating that individuals with compromised respiratory health, such as those with COPD, often exhibit dysregulated immune responses, thereby increasing their susceptibility to various infections [27]. There is a strong correlation (r=0.904, very strong positive correlation, significant at p<0.01) observed between the Vitamin D levels and serum IgG levels in COPD patients (Table 2), suggesting that optimizing Vitamin D levels could potentially bolster humoral immunity and mitigate infection risk in this vulnerable population. The heightened risk of severe outcomes from respiratory infections, including SARS-CoV-2, in COPD patients, enhancing humoral immunity through Vitamin D modulation could offer a critical protective strategy [28]. The observed compromise in humoral immunity among COPD patients makes vaccination adherence even more critical for this vulnerable population to prevent severe exacerbations and improve clinical outcomes [29,30].

CD3 cell counts

The total T lymphocyte (CD3+) count was significantly lower in COPD patients (716.53±167.31 cells/µL) compared to controls (1024.44±219.19 cells/µL), reflecting reduced overall cellular immunity in COPD (t[148]=9.620, p<0.001) (Fig. 4 and Table 1).

CD4 cell counts

A significant reduction in CD4+ T-cell counts was observed in the COPD group (659.33±169.54 cells/µL) compared to the control group (821.23±160.63 cells/µL), suggesting a compromised helper T-cell response (t[148]=5.794, p<0.001) (Fig. 4 and Table 1).

CD8 cell counts

In contrast, CD8+ T-cell counts were significantly elevated in COPD patients (1268.69±229.69 cells/µL) compared to controls (1029.61±133.93 cells/µL), indicating enhanced cytotoxic activity possibly linked to chronic inflammation (t[148]=7.916, p<0.001) (Fig. 4 and Table 1). These findings suggest a potential compensatory mechanism or a heightened immune surveillance state, where increased cytotoxic lymphocytes attempt to counteract persistent viral or bacterial burdens common in COPD [31]. This imbalance in T-cell subsets, characterized by decreased helper T cells and increased cytotoxic T cells, signifies a profound dysregulation of adaptive immunity in COPD, which can impair effective immune responses to new pathogens and contribute to chronic inflammation.

The study shows a strong correlation with Vitamin D levels and CD3 (r=0.839, strong positive correlation, significant at p<0.01), CD4 (r=0.815, strong positive correlation, significant at p<0.01, and CD8 cell (r=−0.877, strong negative correlation, significant at p<0.01), highlighting Vitamin D crucial role in modulating both cellular and humoral immunity in these patients (Table 2). The increase in CD8 levels was notably associated with lower Vitamin D levels, suggesting that Vitamin D deficiency might contribute to the observed T-cell dysregulation in COPD [32]. Moreover, a significant decrease in CD3 and CD4 levels was observed in patients with lower Vitamin D levels, reinforcing the intricate relationship between Vitamin D status and T-cell-mediated immune responses. This highlights a potential area for therapeutic intervention, where Vitamin D supplementation could help restore immune balance by regulating CD8+ T cell proliferation and supporting CD3 and CD4+ T-cell maintenance.

Due to the altered CD4 and CD8 counts, the CD4/CD8 ratio was significantly reduced in COPD patients (0.57±0.28) relative to the control group (0.80±0.16), reflecting immune dysregulation and potential disease severity (t[148]=6.334, p<0.001) (Fig. 5 and Table 1). The CD4/CD8 ratio is a marker for immune activation. It can indicate the balance between helper and cytotoxic T-cell responses, with a lower ratio often correlating with chronic antigenic stimulation and immune exhaustion. This ratio has demonstrated utility in predicting non-AIDS morbidity and mortality, even after accounting for CD4 counts, underscoring its relevance as a prognostic indicator in chronic

inflammatory conditions such as COPD [33]. This altered ratio, potentially exacerbated by Vitamin D deficiency, suggests a persistent state of immune activation and dysregulation that could contribute to the pathogenesis and progression of COPD [34].

CONCLUSION

The present study demonstrated significant alterations in both humoral and cellular immune parameters among patients with COPD compared to healthy controls. Specifically, COPD patients exhibited markedly lower Vitamin D and IgG levels, along with a reduction in total T lymphocytes (CD3+) and helper T cells (CD4+). Conversely, cytotoxic T-cell (CD8+) counts were significantly elevated, resulting in a decreased CD4/CD8 ratio, indicative of immune imbalance and chronic inflammatory status. These findings suggest that immune dysregulation, associated with vitamin D deficiency, impaired humoral immunity, and a shift in T cell subsets, may contribute to the pathogenesis and progression of COPD. Vitamin D deficiency has been shown association with worsening of COPD symptoms; earlier intervention with Vitamin D supplementation can be suggested as a part of treatment and prevention. The immune status was measured and showed significant correlation with Vitamin D levels, so it can be used as a potentialbiomarker and appropriate therapeutic target in patients with COPD.

AUTHORS CONTRIBUTION

All the authors have equal contribution.

CONFLICT OF INTEREST

None.

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None.

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