DOI: 10.1002/pul2.12294

RESEARCH ARTICLE

Pulmonary Circulation Open Access PVRI WILEY

The role of vitamin D in chronic obstructive pulmonary disease with pulmonary hypertension

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Funding information
Science and Technology Project of Agriculture and Social Development of Yinzhou District, Ningbo City, Grant/Award Number: 20222YZQ070013; NINGBO Leading Medical & Health Discipline, Grant/Award Number: 2022-B19

Abstract

Hypoxia pulmonary hypertension (PH) belongs to the third major category in PH classification. Chronic obstructive pulmonary disease (COPD) is a common cause of hypoxia PH. Low serum vitamin D concentration is considered to be a possible risk factor for chronic lung disease; epidemiological studies have found that vitamin D deficiency increases pulmonary artery pressure. Therefore, this study aimed to explore the role of vitamin D levels in COPD and chronic hypoxic PH. This retrospective study selected three groups of people as research subjects, including: Group N: normal control group (people without any chronic lung disease or PH); Group C: patients with COPD, but without PH; Group C + PH: patients with COPD and PH. Vitamin D levels and pulmonary artery pressure were observed in the three groups. Vitamin D levels of the three groups showed statistical differences in every pairwise comparison; the vitamin D level of Group C (20.27 ng/mL) was lower than Group N (23.48 ng/mL), Group C + PH was the lowest (14.92 ng/mL). The levels of vitamin D in the three groups in this study were generally low. Vitamin D is negatively correlated with pulmonary artery systolic blood pressure. Low vitamin D levels may have a certain relationship with the occurrence and development of COPD. Further reductions in vitamin D levels may influence the development of PH in COPD.

KEYWORDS
COPD, hypoxia, pulmonary hypertension, pulmonary systolic pressure (PASP), vitamin D

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is an important chronic respiratory disease with a large number of patients and a high fatality rate. Due to its slow progressive development, it seriously affects the patient's ability to work and quality of life. Pulmonary artery hypertension (PAH) is a serious pulmonary circulation disease characterized by elevated pulmonary circulation pressure; it can be divided into two categories: primary (idiopathic pulmonary hypertension [PH]) and secondary (such as congenital

Abbreviations: COPD, chronic obstructive pulmonary disease; CT, computerized tomography; MPAP, mean pulmonary arterial pressure; PAH, pulmonary artery hypertension; PASP, pulmonary systolic pressure; PH, pulmonary hypertension; RAP, right atrial pressure; RHC, right heart catheterization; V, velocity of tricuspid valve.

heart disease, hypoxic lesions, pulmonary thromboembolism, etc.). Most causes of PH disease are due to secondary, including hypoxia PH which belongs to Group 3 in PH classification.[1] The early phase of pathological process is pulmonary vasoconstriction, chronic phase forms irreversible pulmonary vascular remodeling, leading to a gradual increase in pulmonary vascular resistance and the formation of chronic pulmonary heart disease, resulting in right heart failure and death ultimately.[2] Patients with COPD may develop a series of complications at a certain stage, including chronic hypoxic PH, which further affects the patients' quality of life. The most common lung disease associated with PH is COPD. Given the high prevalence of COPD, probably many thousands of patients with COPD worldwide harbor severe PH, outnumbering patients with pulmonary arterial hypertension (PAH).[3] Currently, there is no particularly effective treatment for COPD accompanied by PH.

Vitamin D is a steroid derivative, meanwhile 1α, 25-dihydroxyvitamin D3 (1α,25(OH)2D3) is the active form of vitamin D. In addition to its classic role in regulating blood calcium balance and bone metabolism, further research has found that vitamin D also plays an important role in immune and respiratory health.[4–9] Low serum vitamin D concentration is considered to be a possible risk factor for chronic lung disease. Several cross-sectional studies have also found that inferior vitamin D levels are associated with reduced lung function. Epidemiological studies have found that vitamin D deficiency increases pulmonary artery pressure.[10] Nevertheless, the relationship between vitamin D and COPD accompanied by PH remains unknown. Therefore, this study aimed to explore the role of vitamin D levels in COPD accompanied by PH.

METHODS

1. Research subjects: This retrospective study selected three groups of people as research subjects, including: Group N: normal control group (people without any chronic lung disease or PH selected from physical examination center); Group C: patients with COPD, but without PH; Group C + PH: patients with COPD and PH. Participants were exempted from signing an informed consent form because personal privacy information was not involved in the study. All were Asian, aged between 46 and 98 years old. Patients were enrolled between January 2020 and July 2022. The ratio of male to female is almost equal. The diagnostic criteria for PH are from the 2022 ESC/ERS Guidelines for the diagnosis and treatment of PH. Mean pulmonary arterial pressure (MPAP) in resting state ≥20 mmHg. Patients with COPD met the criteria for COPD in the Global Strategy for Diagnosis Treatment and Prevention of COPD 2021 (GOLD 2021). People with long-term oral vitamin D supplements or calcium supplements and multivitamins containing vitamin D were excluded initially.
2. Laboratory examination: Vitamin D was detected by ROCHE Cobas E601 electrochemiluminescence analyzer and related reagents, strictly according to the instrument and reagent instructions. PHILIPS HD11 3D color ultrasound was used in Doppler cardiac color ultrasound; the patient was placed in supine position or left decubitus position at rest, and parasternal intercostal exploration was performed on the third to fourth intercostals. The inner diameter of pulmonary artery and left and right pulmonary artery were measured on the short axis section of the main artery. The maximum regurgitation velocity of tricuspid valve (V) was measured by continuous Doppler, PASP = $4V^2$+ right atrial pressure (RAP) was calculated according to the modified Bernoulli equation.[11] In addition, the patients were trained to hold their breath before computerized tomography (CT) scan, then underwent CT scan in supine position with their feet in first. 64-row multislice CT (Philips, B reliance VCT 64) using electrocardiography gate in coronary angiography mode. MPAP = 9.01 + 34.195 * main pulmonary artery (dMPA)/diameters of the ascending aorta (dAA) − 0.319 * systolic blood pressure (SBP) + 0.402 * Cobb angle.[12] In all patients, PASP was first assessed by echocardiography, and then MPAP estimation from CT. PH meets the criteria for both PASP ≥ 30 mmHg and MPAP ≥ 20 mmHg. In all the control groups, PH was excluded (MPAP < 20 mmHg and PASP < 30 mmHg).
3. Statistical analysis: The data were expressed as mean ± SD, median and qua-ternary interval, or percentages. The measurement data were normally distributed, one-way ANOVA was used for comparison between multiple means, and Chi-square test was used for pairwise comparison. $p < 0.05$ was considered a statistically significant difference. Results of continuous variables are presented as mean or median (interquartile range [IQR]), whereas categorical data are shown as absolute

and relative frequency. Multivariable linear regression analysis was conducted to detect the effect of other independent variables on the MPAP. The correlations were evaluated using Pearson and Spearman correlation coefficients. Receiver operating characteristic (ROC) curves were constructed to explore the optimum cutoff value that maximized sensitivity and specificity. To estimate the relationship between vitamin D level and MPAP, a linear regression was done, taking into account the matching for sex and age, BMI, and BP, and was adjusted for smoking status and sunlight exposure. The coefficient of linear correlation was expressed as an r value. Statistical significance was set at $p < 0.05$. The main analysis was performed by SPSS V.22.0 and GraphPad Prism V.8.0.

RESULTS

The flow chart can be seen from Figure 1 that a total of 487 people were considered potentially eligible from January 2020 to July 2022; 24 people who had not been tested for vitamin D and 30 patients who had other plausible causes of PH were excluded, eventuality 433 patients were enrolled in the study (Figure 1). There were 155 patients in Group N, 147 in Group C, and 131 in Group C + PH. The age, sex, sunshine duration, smoking status, vitamin D level, MPAP, and other general information of the three groups are shown in Table 1. Only 15 patients underwent right heart catheterization (RHC); 6 of them were excluded, so the data is too small to be presented here. Data such as age/weight/height/sex/blood pressure/heart rate/WHO functional class/smoking status/sunlight exposure/pulmonary function test/C-reactive protein/25-OH vitamin D were available for 433 people. Data such as GOLD stage of obstruction/NT-proBNP/Blood gas analysis/Therapy/MPAP were available for 308 patients.

As can be seen from Table 2, in the univariate analysis, a large number of noninvasive clinical parameters were associated with PH such as WHO functional class, smoking status, sunlight exposure (>5 h/week and >10 h/week), pulmonary function test, laboratory parameters, therapy (oxygen Inhalation and systemic steroids), and MPAP. In Figure 2, vitamin D levels of the three groups showed statistical differences in every pairwise comparison ($p < 0.05$). The vitamin D level of group N was the highest

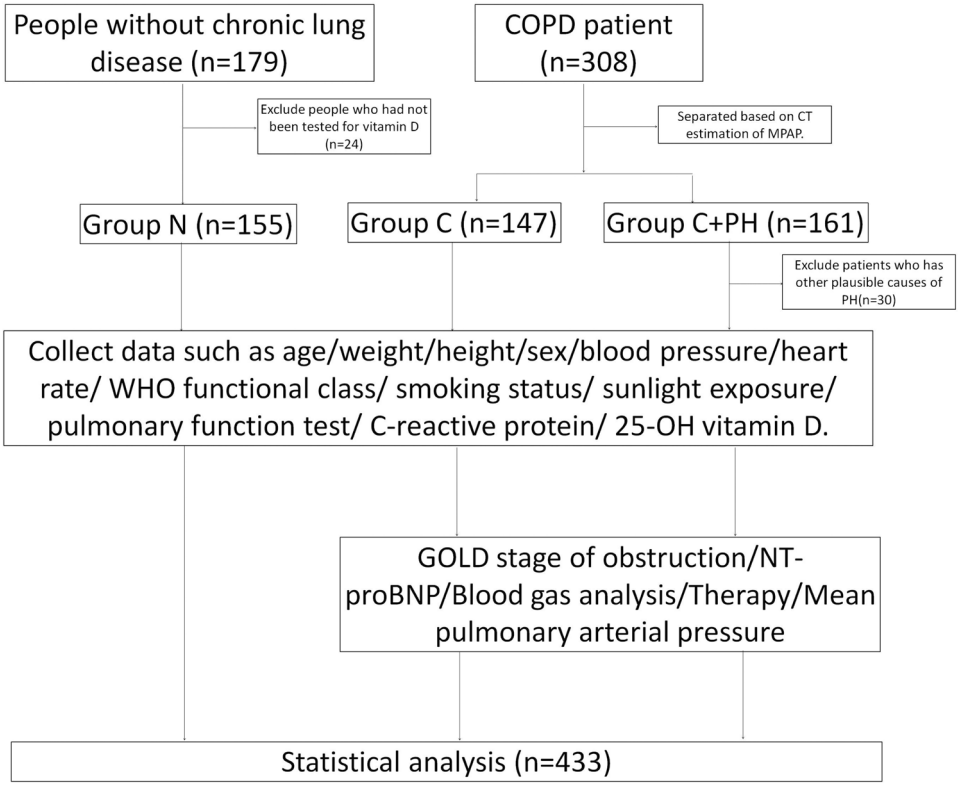

FIGURE 1 Flow chart of this study. Group N: normal control group (people without any chronic lung disease or pulmonary hypertension [PH]); Group C: patients with COPD, but without PH; Group C + PH: patients with COPD and PH. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; WHO, World Health Organization.

TABLE 1 Patient characteristics ($n = 433$).

Characteristic	Data
Age (years)	75 (46–98)
Height (cm)	168 (151–178)
Weight (kg)	61 (47–82)
BMI (kg/m^2)	22.5 (20.3–27.1)
Sex	
Male	236 (55)
Female	197 (45)
BP (mmHg)	
Systolic	112 (97–156)
Diastolic	62 (43–83)
Heart rate	74 (48–112)
WHO functional class	
I	155 (36)
II	147 (34)
III	89 (20)
IV	42 (10)
Smoking status (%)	
Current	210 (48.50)
Former	86 (19.86)
Never	137 (31.64)
Sunlight exposure (%)	
<5 h/week	220 (50.81)
>5 h/week	113 (26.10)
>10 h/week	100 (23.09)
Pulmonary function test	
FEV_1, % predicted	57.0 (44.4–99.9)
FVC, % predicted	76.7 (62.4–96.5)
FEV_1 to FVC ratio (%)	53.6 (42.1–97.6)
GOLD stage of obstruction[a]	
I	36 (13)
II	128 (46)
III	78 (28)
IV	36 (13)
Laboratory parameters	
NT-proBNP, pg/mL[a]	856 (74–3678)
C-reactive protein, mg/L	10.7 (0.4–47.3)
Blood gas analysis[a]	
Arterialized capillary PO_2 (mmHg)	66.3 (47.8–96.5)
Arterialized capillary PCO_2 (mmHg)	41.7 (37.2–92.6)
Therapy[a]	
Oxygen inhalation (%)	178 (64.0)
Systemic steroids (%)	101 (36.3)
Antibiotics (%)	159 (57.2)
25-OH vitamin D (ng/mL)	19.8 (4.03–53.47)
Vitamin D deficiency (<20 ng/mL) (%)	252 (58.19)
Vitamin D insufficiency (20–29 ng/mL) (%)	133 (30.72)
Vitamin D sufficiency (≥30 ng/mL) (%)	48 (11.09)
Pulmonary systolic pressure (mmHg)[a]	44.34 (19–96)
Mean pulmonary arterial pressure (mmHg)[a]	43.22 (17–92)

Note: Data are presented as No. (%) or median (interquartile range), unless otherwise indicated.

Abbreviations: BMI, body mass index; BP, blood pressure; FEV1, Forced Expiratory Volume In 1 s; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO, World Health Organization.

[a]Available for 278 patients.

(23.48 ng/mL). The vitamin D level in Group C + PH was the lowest (14.92 ng/mL). Group C (20.27 ng/mL) was between Group N and Group C + PH (Table 2). The levels of vitamin D in the three groups in this study were generally low, among which the proportion of vitamin D deficiency (<20 ng/mL) was as high as 58.20%, which was particularly obvious in Group C and Group C + PH (Table 1), accounting for 57.14% and 86.26%, respectively. In group N, the number of vitamin D insufficiency (20–29 ng/mL) was higher, accounting for 43.87% (Table 2 and Figure 3).

Taking all these factors into account, Figure 4 mainly describes the correlation between pulmonary artery systolic blood pressure and vitamin D level. Vitamin D negatively correlates with pulmonary artery systolic blood pressure ($r = -0.277$). The lower the vitamin D level, the higher the pulmonary artery systolic pressure after adjustment for potential confounders.

We performed ROC analyses to assess the sensitivity and specificity of vitamin D as predictors for the PH (Figure 5). Vitamin D showed an area under the curve of 0.7389 as a predictor of PH. BNP could also be a predictor of PH with an area under the curve of 0.8418.

To further verify the influence of smoking status on the vitamin D level, we divided the patients into Never/Former/Current smoking status. The p value is significantly different between Never and Former patients. The

TABLE 2 Comparison of clinical and biochemical features of three groups ($n = 433$).

Characteristic	Group N ($n = 155$)	Group C ($n = 147$)	Group C + HP ($n = 131$)	*r* Value
Age (years)	72 (46–89)	74 (51–98)	78 (54–95)	−0.0012
Height (cm)	166 (155–174)	168 (152–178)	169 (153–175)	−0.0043
Weight (kg)	65 (54–82)	60 (47–74)	62 (48–68)	0.0016
BMI (kg/m^2)	23.5 (22.5–27.1)	22.6 (20.3–23.4)	21.6 (20.5–22.2)	0.0013
Sex				
Male	90 (58)	84 (57)	64 (49)	0.0730
Female	65 (42)	63 (43)	67 (51)	−0.0015
BP (mmHg)				
Systolic	115 (100–148)	113 (98–156)	111 (97–140)	0.0026
Diastolic	63 (56–83)	61 (43–80)	62 (45–80)	0.0025
Heart rate	73 (48–110)	74 (52–109)	75 (58–112)	−0.0017
WHO functional class				−0.2310
I	155 (100)	14 (10)	0 (0)	
II	0 (0)	133 (90)	0 (0)	
III	0 (0)	0 (0)	89 (68)	
IV	0 (0)	0 (0)	42 (32)	
Smoking status (%)				−0.2650
Current	25 (16.13)	100 (68.03)	85 (64.89)	
Former	19 (12.26)	34 (23.13)	33 (25.19)	
Never	111 (71.61)	13 (8.84)	13 (9.92)	
Sunlight exposure (%)				0.6710
<5 h/week	79 (50.91)	78 (53.19)	63 (48.39)	
>5 h/week	34 (21.82)	41 (27.66)	38 (29.03)	
>10 h/week	42 (27.27)	28 (19.15)	30 (22.58)	
Pulmonary function test				
FEV_1, % predicted	90.6 (80.2–99.9)	55.6 (44.4–80.6)	53.1 (47.9–78.5)	0.3650
FVC, % predicted	93.2 (85.1–96.5)	73.5 (62.4–82.2)	75.4 (61.7–79.5)	0.1954
FEV_1 to FVC ratio (%)	91.9 (83.3–97.6)	51.9 (43.8–63.2)	58.3 (42.1–67.4)	0.2034
GOLD stage of obstruction[a]				−0.3420
I	N/A	20 (14)	16 (12)	
II	N/A	74 (50)	54 (41)	
III	N/A	32 (22)	46 (35)	
IV	N/A	21 (14)	15 (12)	
Laboratory parameters				
NT-proBNP, pg/mL[a]	N/A	256 (74–466)	923 (278–3678)	−0.1930
C-reactive protein, mg/L	2.5 (0.4–8.9)	12.9 (1.6–47.3)	16.8 (1.3–46.5)	−0.0250

(Continues)

TABLE 2 (Continued)

Characteristic	Group N ($n = 155$)	Group C ($n = 147$)	Group C + HP ($n = 131$)	r Value
Blood gas analysis[a]				
Arterialized capillary PO_2 (mmHg)	N/A	67.9 (47.9–96.5)	65.8 (47.8–94.6)	0.0140
Arterialized capillary PCO_2 (mmHg)	N/A	40.0 (37.2–92.6)	43.2 (38.0–89.2)	−0.0097
Therapy[a]				
Oxygen inhalation (%)	N/A	86 (58.5)	92 (70.2)	−0.0271
Systemic steroids (%)	N/A	47 (32.0)	54 (41.2)	−0.0193
Antibiotics (%)	N/A	80 (54.4)	79 (60.3)	0.0011
25-OH vitamin D (ng/mL)	23.48 (4.03–53.47)	20.27 (7.33–50.92)	14.92 (5.3–46.99)	
Vitamin D deficiency (<20 ng/mL) (%)	55 (35.48)	84 (57.14)	113 (86.26)	
Vitamin D insufficiency (20–29 ng/mL) (%)	68 (43.87)	53 (36.05)	12 (9.16)	
Vitamin D sufficiency (≥30 ng/mL) (%)	32 (20.65)	10 (6.81)	6 (4.58)	
Pulmonary systolic pressure (mmHg)[a]	N/A	24.93 (19–30)	66.13 (31–96)	−0.2890
Mean pulmonary arterial pressure (mmHg)[a]	N/A	18.52 (17–20)	51.01 (31–92)	−0.2770

Note: Data are presented as No. (%) or median (interquartile range), unless otherwise indicated.

Abbreviations: BMI, body mass index; BP, blood pressure; FEV1, Forced Expiratory Volume In 1 s; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO, World Health Organization.

[a]Available for 278 patients.

p value significantly differs between Former and Current smokers (Figure 6). To further verify the influence of vitamin D level on the WHO functional class, we divided the patients into I/II/III/IV four groups. Group I and Group II showed no statistical difference, and Group III and Group IV showed no statistical difference, but the p value significantly differs between Group II and Group III (Figure 7).

We found mild to moderate negative correlations between the plasma vitamin D level and smoking status, WHO functional class, GOLD stage, NT-proBNP, and MPAP in all patients ($p < 0.0001$, Supplemental Figure). There were mild positive correlations between the vitamin D levels and sunlight exposure, FEV_1% predicted ($p = 0.0240$, $p < 0.0001$, Supplemental Figure). There were no significant correlations in the plasma vitamin D levels with CRP ($p = 0.3540$, Supplemental Figure).

DISCUSSION

The role of vitamin D in bone metabolism has been studied for years; recently, researchers at home and abroad have focused on the relationship between vitamin D and autoimmune diseases (such as rheumatoid arthritis, inflammatory bowel disease, etc.), hypertension, heart failure, diabetes, and infectious diseases.[4] Generally, the relationship between vitamin D and pulmonary vascular disease can be mainly reflected in the following three aspects: ①Vitamin D and infectious diseases: 1,25-(OH)D deficiency results in reduced binding of macrophage vitamin D receptors to 1,25-$(OH)_2$ D_3 which leads to the 1,25-$(OH)_2$ D-VDR regulated antimicrobial genes (i.e., antimicrobial peptides) are not fully activated, the killing ability of invading microorganisms was significantly weakened.[5] Vitamin D supplementation could be beneficial in improving resistance to

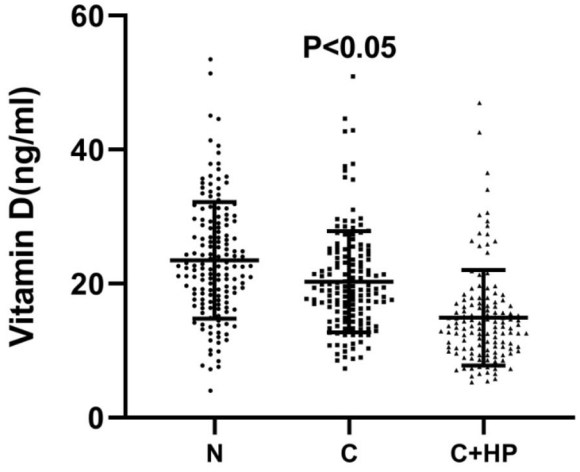

FIGURE 2 Vitamin D levels of the three groups. Group N: normal control group (people without any chronic lung disease or pulmonary hypertension [PH]); Group C: patients with COPD, but without PH; Group C + PH: patients with COPD and PH. COPD, chronic obstructive pulmonary disease.

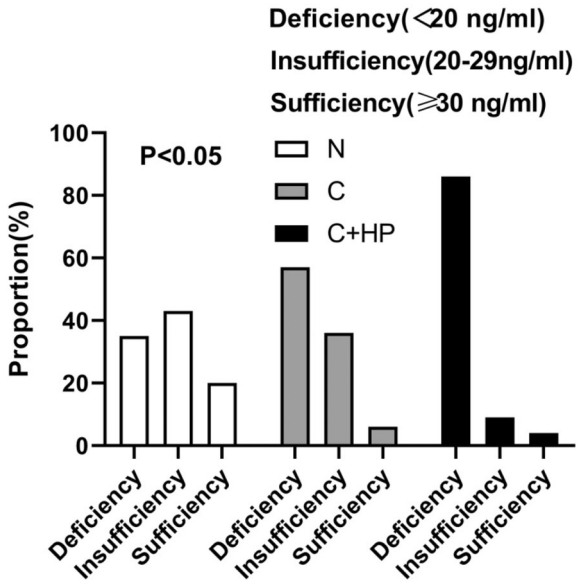

FIGURE 3 The percentage of vitamin D deficiency (<20 ng/mL)/vitamin D insufficiency (20–29 ng/mL)/vitamin D sufficiency (≥30 ng/mL) in three groups. Group N: normal control group (people without any chronic lung disease or pulmonary hypertension); Group C: patients with COPD, but without pulmonary hypertension; Group C + PH: patients with COPD and pulmonary hypertension. COPD, chronic obstructive pulmonary disease.

overall respiratory infections.[13] ②Vitamin D and lung disease: Regression analysis showed a correlation between vitamin D deficiency and asthma, as well as the lower vitamin D content, the more severe the asthma symptoms.[6] Vitamin D levels were significantly associated with lung function (FEV and FVC). Studies on the

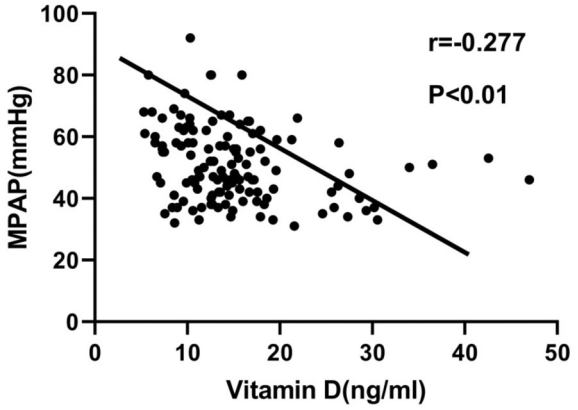

FIGURE 4 The correlation between MPAP and vitamin D level. MPAP, mean pulmonary arterial pressure.

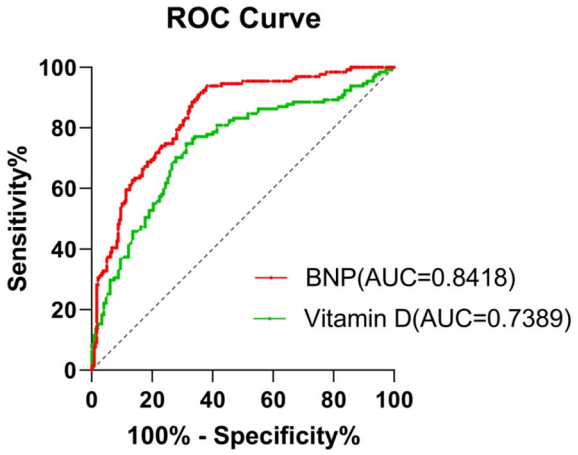

FIGURE 5 ROC analysis of the Group C and Group C + PH based on vitamin D level as a predictor of pulmonary hypertension (PH). Group C: patients with COPD, but without PH; Group C + PH: patients with COPD and PH. BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; ROC, receiver operating characteristic.

level of 25-(OH)-D_3 in COPD patients are not uncommon. ③Vitamin D and cardiovascular disease: Vitamin D has many potential functions, including preservation and protection of vascular endothelium, inhibition of smooth muscle cell proliferation, it protects against changes in the morphology of vascular smooth muscle cells, thus further inhibiting the secretion of inflammatory molecules.[7,8] Demir et al. found that people with vitamin D deficiency had higher pulmonary artery systolic blood pressure than the normal population, which suggests that vitamin D deficiency may be associated with PH.[9] However, this study mainly studied patients with infectious diseases and heart disease, without specific classification of PH, and there are still few studies on the relationship between hypoxic PH and vitamin D.

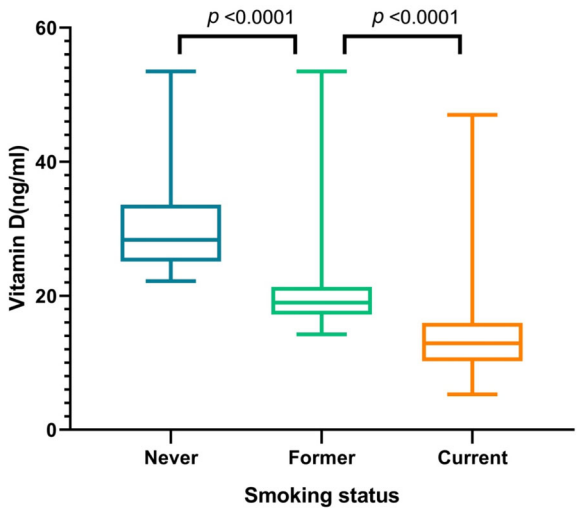

FIGURE 6 Comparison of vitamin D level among Never/Former/Current smoking status.

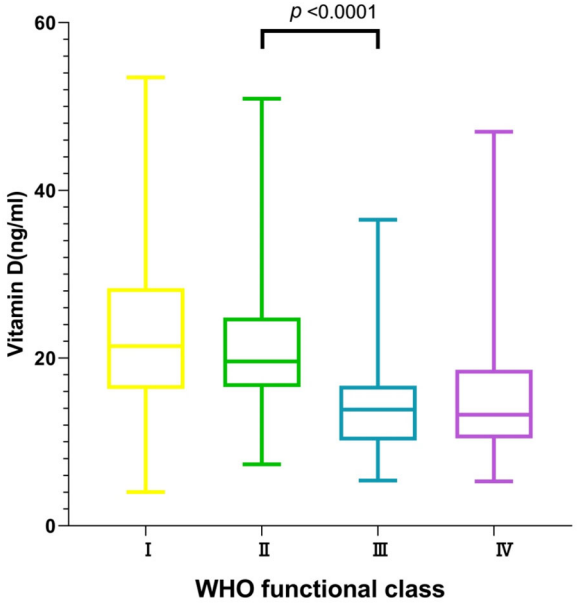

FIGURE 7 Comparison of vitamin D level among patients with different WHO functional classes. WHO, World Health Organization.

We compared three methods for estimating pulmonary artery pressure in our study. RHC is invasive, complicated, and expensive, although RHC is currently the gold standard in clinical diagnosis of PH. It should be noted that certain difficulties can present in operating and interpreting RHC results in older patients, and most of our patients were over 70. Thus, the low number of our RHC data precludes reliable statistical analysis. Whereas echocardiogram can detect the change of pulmonary pressure in patients with PH reflecting variation in the patient's heart function, which is easy to operate, convenient to repeat, and with low expense.[11] However, color Doppler echocardiography lacks accuracy in the diagnosis of mild and moderate PH. Meanwhile, posterior 64-slice CT is more accurate because it has a higher time resolution, its measurement of the large blood vessel diameter was less affected by the heart movement artifact.[12] Therefore, this study mainly used Doppler cardiac color ultrasound combined with CT scan to measure pulmonary artery pressure (PASP and MPAP).

In COPD patients, due to reduced airflow inhalation, limited exhalation, and reduced number of alveoli involved in respiratory exchange, normal gas exchange cannot be carried out, resulting in insufficient oxygen inhalation, poor excretion of metabolic carbon dioxide in the body, and hypoxemia and hypercapnia in patients. The results of this study showed that the vitamin D level of patients with COPD was significantly lower than that of the population without chronic pulmonary disease, suggesting that the low vitamin D level may have a certain relationship with the occurrence and development of COPD. Further reductions in vitamin D levels may lead to the development of PH in COPD. The reasons for this may be related to the decline in lung function caused by vitamin D deficiency: ①Higher vitamin D concentrations are associated with higher lung volume-related spirometric parameters in adolescence.[14] ②The deficiency of vitamin D leads to the body's susceptibility to external pathogens, which increases the number of acute attacks in COPD patients.[15] ③Vitamin D can inhibit the release of pro-inflammatory factors in macrophages and the growth of fibroblasts, thus reducing pulmonary vascular remodeling caused by continuous inflammatory response.[16]

This study found widespread vitamin D deficiency and insufficiency in the population. Vitamin D is a steroid hormone. The main source of vitamin D in the body is 7-dehydrocholesterol in subcutaneous tissue, which is formed by ultraviolet light to form provitamin D_3, and then slowly isomerize into vitamin D_3. It is metabolized to 25-hydroxyvitamin D_3 in the liver and subsequently to 1,25-dihydroxyvitamin D_3 in the kidneys.[17,18] Vitamin D deficiency occurs when there is insufficient daylight and dietary intake. Due to the need for skin protection and appearance, some people reduce the time and area of skin exposure to sunlight by wearing sunscreen and using sunshades. As well as skin aging and weakened synthesis ability. At the same time, vitamin D intake in the diet is relatively insufficient, so people lessen their intake foods rich in vitamin D such as wild fatty fish and fungi. The levels of vitamin D in the three groups in this study were generally low, among which the proportion of vitamin D deficiency (<20 ng/mL)[19] was as high as 58.19%, the prevalence of

vitamin D deficiency in the general population without chronic lung disease may be related to the reasons mentioned above for low vitamin D synthesis and intake. We found that smoking is negatively related to vitamin D levels, which suggests that vitamin D sufficiency may have a protective effect against the damaging effects of smoking on lung function and pulmonary vessels. Similar results of some previous studies reported that vitamin D deficiency was associated with lower lung function and more rapid lung function decline in smokers over 20 years.[20] As well as vitamin D sufficiency may protect against the damaging effects of smoking on coronary arteries.[21] Vitamin D deficiency is particularly evident in COPD patients and COPD patients with PH, which may lead to an increase in the number of acute exacerbations of COPD and the formation of pulmonary vascular disease.

Meanwhile, vitamin D levels were found to be negatively correlated with MPAP. Lower vitamin D levels were associated with higher pulmonary arterial pressure, which may be associated with the cardiopulmonary function of COPD patients. The more severe hypoxia in COPD patients, the more significant pulmonary vascular remodeling, pulmonary arterial pressure is relatively likely to be higher. WHO functional class group III and IV patients had a lower vitamin D level than Group I and Group II, and vitamin D is a predicted factor that is slightly inferior to BNP in PH. Previous studies showed that low vitamin D levels are associated with decreased functional capacity and increased New York Heart Association classes.[22] Thus, vitamin D might be used as a predictor in hypoxia PH patients.

Some research suggested that vitamin D and dexamethasone share many vitamin D receptor pathways,[23] it is still unclear that whether steroid use may affect vitamin D levels. Since the high proportion of subjects with COPD and COPD-PH who are being treated with systemic steroids, this might influence our results. The mechanism of vitamin D in hypoxic PH is still unclear and the lack of RHC data, further major clinical trials and laboratory studies are needed to confirm whether vitamin D deficiency increases the severity of COPD and leads to increased pulmonary pressure, or whether vitamin D deficiency directly affects pulmonary vascular remodeling and leads to PH. The high proportion of current smokers and the high prevalence of vitamin D deficiency may limit the generalizability of the study results.

CONCLUSIONS

This is the first study to explore the relationship between vitamin D and COPD accompanied by PH. COPD patients had a lower vitamin D level than normal people; simultaneously, COPD accompanied by PH had a lower vitamin D level than simple COPD patients. Vitamin D levels were found to be negatively correlated with pulmonary arterial pressure, which may have a hint about the future treatment of chronic hypoxia PH for clinicians.

AUTHOR CONTRIBUTIONS

Mengxi Li designed the study, collected data, and wrote the paper.

ACKNOWLEDGMENTS

Jinhui Li helped me with statistical analysis and chart making. This work was supported by the Science and Technology Project of Agriculture and Social Development of Yinzhou District, Ningbo City, grant number 20222YZQ070013. Funded by the Project of NINGBO Leading Medical & Health Discipline, Project Number: 2022-B19.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from The Affiliated People's Hospital of Ningbo University, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available.

ETHICS STATEMENT

This study was conducted following the guidelines outlined in the Declaration of Helsinki. All procedures involving human subjects were approved by the Medical Ethics Committee of The Affiliated People's Hospital Of Ningbo University; approval number: 2022-026. Participants were exempted from signing an informed consent form because personal privacy information was not involved in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Li M. The role of vitamin D in chronic obstructive pulmonary disease with pulmonary hypertension. Pulm Circ. 2023;13:e12294. https://doi.org/10.1002/pul2.12294