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Correlations of IL-1β and vitamin D with CAT score in patients with acute exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

This study was to analyze the correlations of IL-1β and vitamin D (VitD) with chronic obstructive pulmonary disease assessment test (CAT) score in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). For this purpose, a total of 65 patients with chronic obstructive pulmonary disease (COPD) treated in our hospital between June 2020 and June 2022 were enrolled and assigned to a research group, and 40 healthy individuals who underwent physical examination in our hospital over the same time spanning were enrolled into the control group. The 65 COPD patients were further grouped into a stability group (30 cases) and an exacerbation group (35 cases). The two groups were compared in the levels of 25-hydroxyvitamin D (25(OH)D), interleukin-1β (IL-1β) and blood gas indexes (arterial carbon dioxide partial pressure ($PaCO_2$) and arterial partial pressure of oxygen (PaO_2). The modified Medical Research Council Dyspnea Scale (mMRC) and the CAT were adopted for evaluation of the stability group and exacerbation group. The correlations of IL-1β and 25(OH)D with mMRC and CAT scores were analyzed. The diagnostic value of IL-1β and VitD in patients in different stages was analyzed through receiver operating characteristic (ROC) curves. Results showed that the control group showed greatly lower IL-1β and $PaCO_2$ levels and higher 25(OH)D and PaO_2 levels than the research group (all $P<0.05$). The stability group got greatly lower mMRC and CAT scores than the exacerbation group (both $P<0.05$). IL-1β had positive correlations with mMRC and CAT scores, while 25(OH)D had negative correlations with them ($P<0.05$). According to ROC curve-based analysis, IL-1β and 25(OH)D had areas under the curves of 0.814 and 0.583, respectively, in diagnosing the acute exacerbation period, and had specificities of 56.67% and 43.33%, respectively and sensitivities of 97.14% and 74.29%, respectively. In conclusion, patients with COPD have increased IL-1 β and VitD deficiency, so VitD can be properly supplemented during treatment, and the levels of inflammatory factors should be paid close attention to at all times. IL-1 β and VitD can be regarded as novel ideas for the diagnosis and treatment of COPD, which may further improve the effect of COPD prevention and treatment.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a frequently-seen, preventable and treatable chronic airway inflammatory disease, with features of incomplete reversible airflow limitation and corresponding respiratory symptoms (1). Its early symptoms include repeated cough and expectoration, and even dyspnea in severe cases (2). Although the disease is an airway disease, its impact on the whole body system should not be underestimated (3). According to the statistical results, COPD afflicts approximately 100 million patients in China in 2018, with a prevalence rate of 8.6% among individuals over 20 years old and a prevalence rate of 13.7% among individuals over 40 years old, and it ranks third in the cause of death in 2020 (4). COPD has become a major disease like hypertension and diabetes mellitus, and its burden has ranked third (5). The disease can be classified into COPD at the stable stage and COPD at the acute exacerbation stage according to the disease process. The symptoms in the stable period are mild, while the clinical symptoms in the acute exacerbation period continue to deteriorate, mainly manifested as cough, expectoration, shortness of breath or wheezing, and increased sputum volume, accompanied by fever and other symptoms of aggravated inflammation.

Currently, the clinical research on acute exacerbation of COPD (AECOPD) has made progress, but there is still a lack of clear indicators for the prevention, diagnosis, treatment and prognosis of it, which may delay the optimal treatment timing (6) Therefore, it is still imperative to find appropriate associated indicators to prevent and treat patients with AECOPD, so as to effectively avoid or reduce acute attacks and achieve the optimal treatment effect. Interleukin-1β (IL-1β) is a pro-inflammatory cytokine involved in host defense responses like immune response, inflammation, fever and acute protein synthesis, which can trigger pulmonary inflammation featured with granulocyte and macrophage infiltration in the lung (7). Reportedly, the increased IL-1β expression may be adopted as a biomarker of persistent neutrophil airway inflammation and potential persistent deterioration in COPD (8). Vitamin D (VitD) is a frequently-seen fat-soluble vitamin, with a crucial role in the growth and development of the body and cell growth and differentiation (9). Its main form is 25-hy-

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droxyvitamin D (25(OH)D), which is usually adopted to evaluate the VitD level in the human body. According to prior research (10), VitD can not only regulate calcium and phosphorus metabolism, but is also bound up with respiratory system and lung function, and its deficiency may impair lung function and increase the risk of respiratory tract infection.

AECOPD does great harm to patients' life and health and will cause a series of adverse reactions, seriously compromising patients' quality of life. Accordingly, this study explored the correlations of IL-1β and VitD with chronic obstructive pulmonary disease assessment test (CAT) scores in patients with AECOPD, to provide a reference for clinical diagnosis and treatment of the disease.

Materials and Methods

Clinical data

Totally 65 patients with COPD treated in our hospital between June 2020 and June 2022 were enrolled and assigned to a research group, and 40 healthy individuals who underwent physical examination in our hospital over the same time spanning were enrolled in the control group. The 65 COPD patients were further grouped into a stability group (30 cases) and an exacerbation group (35 cases). This study was performed with approval from the Medical Ethics Committee of our hospital.

Inclusion and exclusion criteria

Inclusion criteria

Patients in the research group all met the diagnostic criteria of COPD (11), and the criteria for judging the severity are shown in Table 1. Patients at the I-II stage were assigned to a stability group, and those at the III-IV stage were assigned to an exacerbation group. Individuals in the control group were all healthy individuals without any disease. All subjects voluntarily participated in this study and signed informed consent, and their clinical data were complete.

Exclusion criteria

Terminally ill patients were comorbid with malignant tumour or other diseases; patients with diabetes mellitus or heart, liver or renal failure; patients with mental disorders, patients who withdrew from the study midway, and pregnant women.

Index detection method

Fasting peripheral venous blood (6mL) was acquired from each participant, and let to stand at indoor temperature (2-4 h), followed by 20-min centrifugation (3000r/min). Then the serum was collected, and stored at low temperature for testing. 25(OH)D and IL-1β in the serum were quantified using the immunosorbent assay under strict instructions. An automatic blood gas analyzer was adopted for the determination of the blood gas indexes of each individual, including arterial carbon dioxide partial pressure ($PaCO_2$) and arterial partial pressure of oxygen (PaO_2).

Outcome measures

Primary outcome measures: The 25(OH)D and IL-1β levels of the two groups were compared, and the correlations of IL-1β and 25(OH)D with mMRC and CAT scores were analyzed.

Secondary outcome measures: The blood gas indexes including PaO_2 and $PaCO_2$ were compared between the patients and healthy individuals. The modified Medical Research Council Dyspnea Scale (mMRC) was adopted for assessment of patients' dyspnea: 0 points: mild; 1 point: moderate; 2 points: severe; 3-4 points: extremely severe. The CAT was adopted for the self-assessment test of patients with AECOPD. The test score ranges between 0 and 40 points, with 0-10 points for slight impact, 11-20 points for moderate impact; 21-30 points for serious impact and 31-40 points for extremely serious impact.

Statistical analyses

This study adopted SPSS 20.0 (SPSS Inc., Chicago, IL, USA) for analysis of collected data, and GraphPad Prism 8 for data visualization. The data of this study were normally distributed and were analyzed via the t-test. The correlations of different variables were analyzed using the Pearson test. $P<0.05$ implies a notable difference.

Results

Baseline data

According to the comparison of clinical data, the control and research groups were similar in age, gender, body mass index (BMI), smoking history and drinking history (all $P>0.05$, Table 2).

IL-1β and VitD levels

According to the comparison of IL-1β and VitD levels between the two groups, the control group showed a greatly lower IL-1β level and a notably higher 25(OH)D level than the research group (both $P<0.05$, Figure 1).

Table 1. Severity grading.

Severity grading	Evaluation criteria
Grade I (mild)	$FEV_1 \geq 80\%$ predicted value; have no obvious symptoms or mild symptoms.
Grade II (Moderate)	50% predicted value $\leq FEV_1 < 80\%$ predicted value; have obvious chronic cough and expectoration.
Grade III (Severe)	30% predicted value $\leq FEV_1 < 50\%$ predicted value; have chronic cough, expectoration, dyspnea, etc.
Grade IV (extremely severe)	$FEV_1 < 30\%$ predicted value or $FEV_1 < 50\%$ predicted value, accompanied by respiratory failure; have severe dyspnea and hypoxemia according to test results.

FEV_1: Forced expiratory volume in 1 second.

Table 2. Baseline data.

Factors		Control group (n=40)	Research group (n=65)	χ2 value	P value
Age					
	≤65 years old	23	31	0.953	0.328
	>65 years old	17	34		
Gender					
	Male	25	39	0.065	0.798
	Female	15	26		
BMI					
	≤23kg/m2	23	28	2.062	0.151
	>23kg/m^2	17	37		
Smoking history					
	Yes	22	36	0.001	0.969
	No	18	29		
Drinking history					
	Yes	29	47	0.000	0.982
	No	11	18		

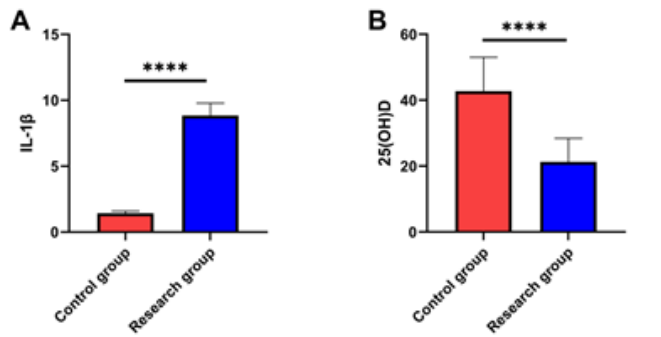

Figure 1. IL-1β and VitD levels. A. Comparison of IL-1β level, B. Comparison of VitD level.

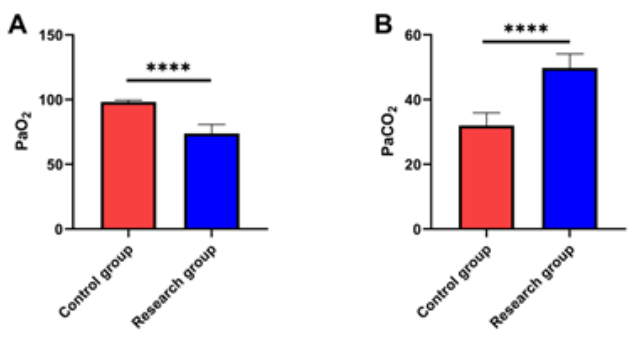

Figure 2. Blood gas index level. A. Comparison of PaO_2 level, B. Comparison of $PaCO_2$ level.

Blood gas index levels

According to analysis and comparison of blood gas indexes between the two groups, the control group showed a greatly higher PaO_2 level and a greatly lower $PaCO_2$ level than the research group (both P<0.05, Figure 2).

mMRC and CAT scores of the stability group and exacerbation group

According to the analysis and comparison of mMRC and CAT scores between the stability group and exacerbation group, the stability group got greatly lower mMRC and CAT scores than the exacerbation group (both P<0.05, Figure 3).

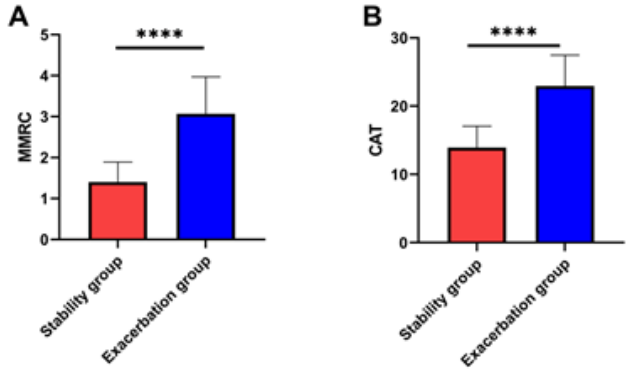

Figure 3. mMRC and CAT scores of the stability group and exacerbation group. A. Comparison of mMRC scores, B. Comparison of CAT scores.

Correlations of IL-1β and 25(OH)D with mMRC and CAT scores

The Pearson test was carried out on the correlations of IL-1β and 25(OH)D with mMRC and CAT scores. According to the results, IL-1β had positive correlations with mMRC and CAT scores, while 25(OH)D had negative correlations with them (all P<0.05, Figure 4).

Clinical diagnostic value of IL-1β and 25(OH)D for AECOPD

For understanding the diagnostic value of L-1β and 25(OH)D for AECOPD, receiver operating characteristic (ROC) curves were drawn. According to ROC curve-based analysis, IL-1β and 25(OH)D had areas under the curves (AUCs) of 0.814 and 0.583, respectively, in diagnosing AECOPD, and had specificities of 56.67% and 43.33%, respectively, and sensitivities of 97.14% and 74.29%, respectively, in it (Table 3 and Figure 5).

Discussion

Over the past few years, COPD presents an increasing incidence and is the most frequently seen among individuals over 40 years old (12). It usually results in the progressive decline of lung function, finally increasing morta-

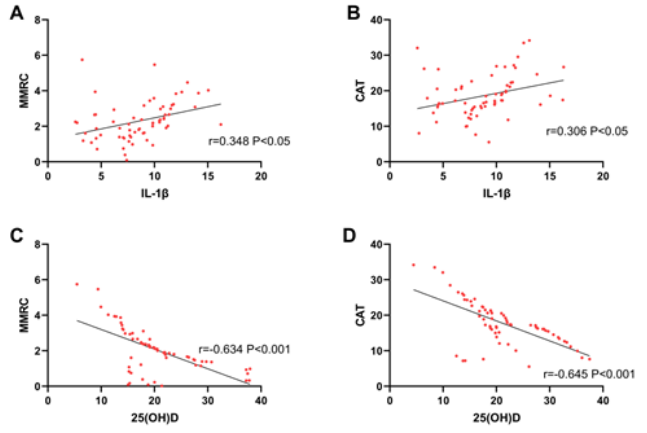

Figure 4. Correlations of IL-1β and 25(OH)D with mMRC and CAT scores. A. Correlation of IL-1β with mMRC score, B. Correlation of IL-1β with CAT score, C. Correlation of 25(OH)D with mMRC score, D. Correlation of 25(OH)D with CAT score.

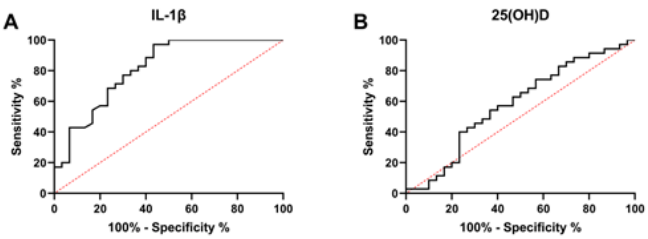

Figure 5. ROC curves of IL-1β and 25(OH)D in the diagnosis of AECOPD.

lity and disability, which seriously compromises the quality of life of patients. COPD is a chronic inflammatory disease of the lung, but its harm to the human body should not be underestimated (13). When the disease develops to acute exacerbation, patients will suffer more serious expectoration, asthma and dyspnea than usual, and patients in severe cases may have pulmonary heart disease and respiratory failure if they are not given timely treatment (14). According to the analysis results of patients' blood gas indexes in this study, the control group presented a notably higher PaO_2 level and a notably lower $PaCO_2$ level than the research group, indicating that long-term weakening of lung function will lead to CO_2 retention and hypoxemia, and the disease aggravation during acute exacerbation will lead to severe hypoxia and respiratory failure, increasing the risk of death. According to associated research (15), during every period of AECOPD, the patients showed a more severe decline of FEV_1 than those with normal lung function, implying the side impacts of the disease on the lung function of patients. Accordingly, it is of profound significance to find suitable associated indexes for the diagnosis and treatment of COPD.

Currently, the pathogenesis of COPD is still under investigation. It is generally believed that its pathogenesis mainly involves inflammatory reactions, the imbalance between oxidation and antioxidation. Airflow restriction and airway obstruction are the most crucial pathophysiological changes in COPD cases, but the specific mechanism leading to airway and pulmonary vascular inflammation remains unclear (16). According to related research (17), patients with AECOPD and respiratory failure showed notably different levels of serum TNF-α and other inflammatory mediators before and after treatment, indicating a strong association of COPD with inflammatory mediators. IL-1β, also known as a catabolic factor, is produced by activated macrophages in the form of pro-protein and belongs to the interleukin-1 cytokine family (18). IL-1β is a crucial mediator of inflammatory reactions and takes part in various cell activities, including cell differentiation, proliferation as well as apoptosis. This study analyzed and compared the IL-1β level in the two groups and revealed a notably lower IL-1β level in the control group than that in the research group, indicating a notable increase of IL-1β in patients with COPD, which was a crucial factor leading to the occurrence and aggravation of the disease. The results are similar to the research results of Li et al. (19). In addition, according to related studies (20,21), VitD deficiency will also impact lung function. Therefore, this study also analyzed the VitD level in participants, and revealed a notably higher 25(OH)D level in the control group than that in the research group, indicating a severe decrease in VitD level in patients with COPD, which may be bound up with the fact that the damaged liver and kidney function in patients with COPD impacts the synthesis of VitD.

Table 3. Clinical diagnostic value of IL-1β and 25(OH)D for AECOPD.

Factors	IL-1β	25(OH)D
AUC	0.814	0.583
Confidence interval	0.708-0.919	0.441-0.725
Specificity	56.67	43.33
Sensitivity	97.14	74.29
Youden index	53.81	17.62
Cut-off	>0.070	>17.92

Currently, the severity of COPD is mainly assessed via the mMRC and CAT (22,23). In this study, the stability group got greatly lower mMRC and CAT scores than the exacerbation group. In addition, the correlation analysis of IL-1β and 25(OH)D with mMRC and CAT scores revealed positive associations of IL-1β with mMRC and CAT scores and negative associations of 25(OH)D with mMRC andCAT scores, which indicated correlations of IL-1β and VitD with the severity of patients' illness. Related studies have also revealed that VitD deficiency and up-regulation of IL-1β expression are bound up with the development and progression of COPD and will damage the lung function of patients (24,25), which is similar to the results of this study. Finally, this study analyzed the ROC curves of IL-1 β and VitD. According to ROC curve-based analysis, IL-1β and25(OH)D had AUCs of 0.814 and 0.583, respectively, in diagnosing AECOPD, and had specificities of 56.67% and 43.33%, respectively, and sensitivities of 97.14% and 74.29%, respectively, in it. The results imply that IL-1 β and VitD can be adopted as reference indexes for the diagnosis and treatment of COPD.

This study has determined the diagnostic value of IL-1β and VitD and their correlations with mMRC and CAT scores. However, it still has some limitations. The sample size collected in this study is limited, so the samples are not uniform like that in the randomized controlled experiment. Therefore, we hope to carry out more experiments in the follow-up research to improve the research conclusions.

To sum up, patients with COPD have increased IL-1 β and VitD deficiency, so VitD can be properly supple-

mented during treatment, and the levels of inflammatory factors should be paid close attention to at all times. IL-1 β and VitD can be regarded as novel ideas for the diagnosis and treatment of COPD, which may further improve the effect of COPD prevention and treatment.

References

1. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet 2017 May 13; 389(10082): 1931-1940. https://doi.org/10.1016/s0140-6736(17)31222-9
2. Labaki WW, Rosenberg SR. Chronic Obstructive Pulmonary Disease. Ann Intern Med 2020 Aug 4; 173(3): ITC17-ITC32. https://doi.org/10.7326/AITC202008040
3. Ritchie AI, Wedzicha JA. Definition, Causes, Pathogenesis, and Consequences of Chronic Obstructive Pulmonary Disease Exacerbations. Clin Chest Med 2020 Sep; 41(3): 421-438. https://doi.org/10.1016/j.ccm.2020.06.007
4. Fang L, Gao P, Bao H, Tang X, Wang B, Feng Y, Cong S, Juan J, Fan J, Lu K, Wang N, Hu Y, Wang L. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. Lancet Respir Med 2018 Jun; 6(6): 421-430. https://doi.org/10.1016/S2213-2600(18)30103-6
5. Duffy SP, Criner GJ. Chronic Obstructive Pulmonary Disease: Evaluation and Management. Med Clin North Am 2019 May; 103(3): 453-461. https://doi.org/10.1016/j.mcna.2018.12.005
6. Mathioudakis AG, Janssens W, Sivapalan P, Singanayagam A, Dransfield MT, Jensen JS, Vestbo J. Acute exacerbations of chronic obstructive pulmonary disease: in search of diagnostic biomarkers and treatable traits. Thorax 2020 Jun; 75(6): 520-527. https://doi.org/10.1136/thoraxjnl-2019-214484
7. Weber A, Wasiliew P, Kracht M. Interleukin-1beta (IL-1beta) processing pathway. Sci Signal 2010 Jan 19; 3(105):cm2. https://doi.org/10.1126/scisignal.3105cm2
8. Zou Y, Chen X, Liu J, Zhou DB, Kuang X, Xiao J, Yu Q, Lu X, Li W, Xie B, Chen Q. Serum IL-1β and IL-17 levels in patients with COPD: associations with clinical parameters. Int J Chron Obstruct Pulmon Dis 2017 Apr 24; 12: 1247-1254. https://doi.org/10.2147/COPD.S131877
9. Kulda V. [Vitamin D metabolism]. Vnitr Lek 2012 May; 58(5): 400-404.
10. Janssens W, Mathieu C, Boonen S, Decramer M. Vitamin D deficiency and chronic obstructive pulmonary disease: a vicious circle. Vitam Horm 2011; 86: 379-399. https://doi.org/10.1016/B978-0-12-386960-9.00017-4
11. Nici L, Mammen MJ, Charbek E, Alexander PE, Au DH, Boyd CM, Criner GJ, Donaldson GC, Dreher M, Fan VS, Gershon AS, Han MK, Krishnan JA, Martinez FJ, Meek PM, Morgan M, Polkey MI, Puhan MA, Sadatsafavi M, Sin DD, Washko GR, Wedzicha JA, Aaron SD. Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 201: e56-e69. https://doi.org/10.1164/RCCM.202003-0625ST
12. Cortopassi F, Gurung P, Pinto-Plata V. Chronic Obstructive Pulmonary Disease in Elderly Patients. Clin Geriatr Med 2017 Nov; 33(4): 539-552. https://doi.org/10.1016/j.cger.2017.06.006
13. Berg K and Wright JL. The Pathology of Chronic Obstructive Pulmonary Disease: Progress in the 20th and 21st Centuries. Arch Pathol Lab Med 2016 Dec; 140(12): 1423-1428. https://doi.org/10.5858/arpa.2015-0455-RS
14. Horodinschi RN, Bratu OG, Dediu GN, Pantea Stoian A, Motofei I and Diaconu CC. Heart failure and chronic obstructive pulmonary disease: a review. Acta Cardiol 2020 Apr; 75(2): 97-104. https://doi.org/10.1080/00015385.2018.1559485
15. Celli BR, Anderson JA, Cowans NJ, Crim C, Hartley BF, Martinez FJ, Morris AN, Quasny H, Yates J, Vestbo J, Calverley PMA. Pharmacotherapy and Lung Function Decline in Patients with Chronic Obstructive Pulmonary Disease. A Systematic Review. Am J Respir Crit Care Med 2021 Mar 15; 203(6): 689-698. https://doi.org/10.1164/rccm.202005-1854OC
16. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. Lancet Respir Med 2022 May; 10(5): 497-511. https://doi.org/10.1016/S2213-2600(21)00506-3
17. Gane JM, Stockley RA, Sapey E. The rs361525 polymorphism does not increase production of tumor necrosis factor alpha by monocytes from alpha-1 antitrypsin deficient subjects with chronic obstructive pulmonary disease - a pilot study. J Negat Results Biomed 2015 Dec 1; 14: 20. https://doi.org/10.1186/s12952-015-0039-3
18. Lopez-Castejon G, Brough D. Understanding the mechanism of IL-1beta secretion. Cytokine Growth Factor Rev 2011 Aug; 22(4): 189-195. https://doi.org/10.1016/j.cytogfr.2011.10.001
19. Li Z, He P, Ding H, Gong L, Wu J, Zhong C, Liu D. Association between peripheral blood WBCs C3aR mRNA level and plasma C3a, C3aR, IL-1beta concentrations and acute exacerbation of chronic obstructive pulmonary disease. Immunobiology 2022 Jan; 227(1): 152164. https://doi.org/10.1016/j.imbio.2021.152164
20. Rafiq R, Aleva FE, Schrumpf JA, Daniels JM, Bet PM, Boersma WG, Bresser P, Spanbroek M, Lips P, van den Broek TJ, Keijser BJF, van der Ven A, Hiemstra PS, den Heijer M, de Jongh RT, group PR-s. Vitamin D supplementation in chronic obstructive pulmonary disease patients with low serum vitamin D: a randomized controlled trial. Am J Clin Nutr 01 Aug 2022; 116(2): 491-499. https://doi.org/10.1093/ajcn/nqac083
21. Mullin MLL, Milne S. Vitamin D deficiency in chronic obstructive pulmonary disease. Curr Opin Pulm Med 2023 Mar 1; 29(2): 96-103. https://doi.org/10.1097/MCP.0000000000000935
22. Deng M, Yin Y, Zhang Q, Zhou X, Hou G. Identification of Inflammation-Related Biomarker Lp-PLA2 for Patients with COPD by Comprehensive Analysis. Front Immunol 2021 May 21; 12: 670971. https://doi.org/10.3389/fimmu.2021.670971
23. Lin L, Song Q, Cheng W, Liu C, Zhao YY, Duan JX, Li J, Liu D, Li X, Chen Y, Cai S, Chen P. Comparation of predictive value of CAT and change in CAT in the short term for future exacerbation of chronic obstructive pulmonary disease. Ann Med 2022 Dec; 54(1): 875-885. https://doi.org/10.1080/07853890.2022.2055134
24. Lokesh KS, Chaya SK, Jayaraj BS, Praveena AS, Krishna M, Madhivanan P, Mahesh PA. Vitamin D deficiency is associated with chronic obstructive pulmonary disease and exacerbation of COPD. Clin Respir J 2021 Apr; 15(4): 389-399. https://doi.org/10.1111/crj.13310
25. Wang YX, Ji ML, Jiang CY, Qian ZB. Upregulation of ICAM-1 and IL-1beta protein expression promotes lung injury in chronic obstructive pulmonary disease. Genet Mol Res 2016 Aug 19; 15(3). https://doi.org/10.4238/gmr.15037971