RESEARCH ARTICLE

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The Effect of Vitamin D Level on the Clinical Situation in COVID-19 Patients

ABSTRACT

Objective: Vitamin D plays an important role in maintaining the integrity of mucosal barriers and in natural and acquired immunity. In the COVID-19 pandemic, the strength of personal immunity is very important in the course of the disease, despite the presence of variants of the virus or vaccination status.

Method: In this study, we investigated the relationship between the clinical course and vitamin D levels of outpatient and inpatient follow-up patients admitted to our hospital due to COVID-19. A total of 94 patients, 47 outpatients and 47 inpatients, were included in the study.

Results: The mean age and gender distributions of both groups were similar. Vitamin D levels were found to be normal in only 7 of 94 patients who were followed up in our hospital due to COVID-19. Patients with vitamin D levels ≥30 were significantly lower than those with "<10" and "10-29.9" ($p<0.01$ for each). Hospitalized patients (71%) with vitamin D levels <10 were significantly higher than those (0%) with vitamin D levels ≥30. Additionally, the outpatients (29%) with vitamin D levels <10 were significantly lower than those (100%) with vitamin D levels ≥30.

Conclusion: The data showed that vitamin D deficiency may be associated with the severe clinical course of COVID-19, even in patients without comorbidities, and may also be one of the predisposing factors resulting in death in COVID-19. As a result, vitamin D levels in COVID-19 patients may be important for the course of the disease.

Keywords: Vitamin D, COVID-19, Clinical Course, Inpatients, Outpatients.

COVID-19 Hastalarında D Vitamini Düzeyinin Klinik Durumla Olan İlişkisi

ÖZET

Amaç: Vitamin D, mukozal bariyerlerin bütünlüğünün korunmasında, doğal ve kazanılmış bağışıklıkta önemli rol oynar. COVID-19 pandemisinde, virüsün varyantlarının varlığına veya aşılanma durumuna rağmen, kişisel bağışıklığın gücü hastalığın seyrinde çok önemlidir.

Gereç ve Yöntem: Bu çalışmada hastanemize COVID-19 nedeniyle başvuran ayaktan ve yatarak tedavi gören hastaların klinik seyri ile D vitamini düzeyleri arasındaki ilişkiyi araştırdık. 47 ayaktan ve 47 yatan hasta olmak üzere toplam 94 hasta çalışmaya dahil edildi.

Bulgular: Her iki grubun ortalama yaş ve cinsiyet dağılımları benzerdi. Hastanemizde COVID-19 nedeniyle takip edilen 94 hastanın sadece 7'sinde D vitamini seviyeleri normal bulundu. D vitamini düzeyi ≥30 olan hastalar, "<10" ve "10-29.9" olanlardan anlamlı derecede düşüktü (her biri için $p<0.01$). D vitamini düzeyi <10 olan hastanede yatan hastalar (%71), D vitamini düzeyi ≥30 olanlardan (%0) anlamlı olarak daha yüksekti. Ek olarak, D vitamini düzeyi <10 olan ayaktan hastalar (%29), D vitamini düzeyi ≥30 olanlardan (%100) anlamlı olarak daha düşüktü.

Sonuç: Veriler, D vitamini eksikliğinin komorbiditesi olmayan hastalarda bile COVID-19'un şiddetli klinik seyri ile ilişkili olabileceğini ve ayrıca COVID-19'da ölümle sonuçlanan predispozan faktörlerden biri olabileceğini gösterdi. Sonuç olarak, COVID-19 hastalarındaki D vitamini seviyeleri hastalığın seyri açısından önemli olabilir.

Anahtar Kelimeler: D Vitamini, COVID-19, Klinik Seyir, Yatan Hastalar, Ayaktan Hastalar.

INTRODUCTION

Severe acute respiratory distress syndrome (ARDS), oxygen desaturation, inflammation, cytokine storm, pneumonia, thrombi/embolism formation and oxidative damage occur as common symptoms in 2019 coronavirus disease (COVID-19) (1). While immune responses specific to COVID-19 are extremely important to eliminate the spread of the virus, uncontrolled inflammatory reactions can trigger systemic damage, especially in the lungs. COVID-19 causes significantly increased morbidity and mortality by causing microvascular thrombosis, oxygen desaturation, differences in lymphocyte and platelet counts and deviations in C-reactive protein and many plasma/serum enzyme levels (2).

Vitamin D is an essential part of the human diet. İt is obtained by skin exposure to sunlight (thereby converting 7-dehydrocholesterol to cholecalciferol, vitamin D3), from foods, or through supplements (3). Vitamin D exists in several forms including 25-hydroxyvitamin D [25(OH)D], the primary circulating form, and 1,25-dihydroxyvitamin D [1,25(OH)2D], the active form (4). Serum 25(OH)D correlates with overall vitamin D stores and is the most commonly used biomarker for assessing vitamin D deficiency. Deficiency is often defined by circulating 25(OH)D levels below 30 ng/ml (75 nmol/l) (5).

Randomized clinical studies have reported effects of vitamin D supplementation in protecting against colds and influenza (6). There are indications of vitamin D being a potent immunomodulator and protective against acute viral respiratory tract infections (7). In recent years, it has been shown that there may be a relationship between COVID-19 infection and vitamin D levels (8). For example, it has been suggested that maintaining optimum levels of vitamin d, thanks to its immunosuppressive effects, may affect the severity of the disease in COVID-19 patients (9). From our literature review, we observed that there are many advantages of prophylactic and therapeutic use of vitamin D in the management of COVID-19 (10).

In this study, we aimed to investigate the effect of vitamin D on clinical status and course in COVID-19 patients.

MATERIAL AND METHODS

Study Design: This study was conducted at Faculty of Medicine in Duzce University between April 01, 2021–May 30, 2021. With the decision number: 2021/157 Clinical Research Ethics Committee at Duzce University approved this study.

We investigated the presence of the Vitamin D's role on the clinical condition in COVID-19 patients. Only the patients admit for COVID to the hospital with positive SARS CoV 2 PCR test (Bio-speedy® SARS CoV-2 RT-qPCR, Turkey) were included in the study. Among the patients included in the study, regardless of COVID-19, they were not receiving vitamin D therapy. In the patients having mild symptoms; normal lymphocyte counts and C reactive protein (CRP) levels and also their oxygen saturation levels were mentioned as in the outpatient group. The patients having severe clinical symptoms were demonstrated among those of whom were hospitalized. In this group, the measurement of lymphocyte counts and O_2 saturation levels were lower than normal. Besides their CRP levels were higher than normal. All cases were divided in two groups as outpatients and inpatients, according to their clinical and laboratory data. Frankly, all those of all patients' blood were obtain on the first and /or third day of their admission to the hospital. The patients' serum samples for measure vitamin D level were stored at -20°C till they were analyzed. Serum vitamin D levels were measured by immunoassay method with Architect 25-OH vitamin D kit (Abbott Diagnostics, Lake Forest, IL, USA). Deficiency is 25(OH)D levels below 30ng/ml (75nmol/l). The patients were divided into 3 groups (<10, 10-29.9, ≥30) according to their vitamin D levels. Considering the detection limits in the laboratory, a vitamin D level of <10 ng/ml indicates low vitamin D levels, a range of 10-29.9 ng/ml is the normal reference value, and a value of ≥30 ng/ml indicates a high level of vitamin D. Lymphocyte counts ≤0.82 ($\times 10^9$/L), mean oxygen saturation (SaO_2) <94, CRP >0.5, ferritin >150ng/ml and D-dimer >0.5 µg/ml were abnormal levels. Presence of diabetes mellitus, hypercholesterolemia/hyperlipidemia, chronic kidney disease, heart failure, coronary and peripheral artery disease were accepted as comorbidity. In addition, CRP (>10), ferritin (>500ng/ml), lymphocyte (<800/µl), D-dimer (>1000ng/ml), oxygen saturation (<93%) and lung involvement by radiological imaging were evaluated as poor prognostic factors.

Radiological Examination: Chest CT images were obtained using a 128-slice multidetector scanner (Somatom definition AS 128, Siemens Healthineers, Erlangen, Germany) with a slice thickness of 1 mm. Both lung (width, 1500 HU; level, -500 HU) and mediastinal (width, 350 HU; level, 40 HU) settings were used in the CT evaluation. Peripheral, bilateral, GGO with or without consolidation or visible interlobular lines (crazy-paving), multifocal GGO of rounded morphology with or without consolidation or visible interlobular lines (crazy-paving) were considered as typical CT findings of COVID-19 on chest CT according to the recommendations of Radiological Society of North America (RSNA) (11).

The presence of multifocal patchy and/or confluent ground glass opacities and consolidations with rounded morphology and coarse horizontal

lines in a bilateral, peripheral and mid to lower zone distribution were considered as highly suggestive findings of COVID-19 on a chest X ray (12).

Statistical Analysis: One Way ANOVA was used for comparison between groups in terms of quantitative variables. Relationships between categorical variables were examined with Pearson Chi-square and Fisher-Freeman-Halton (post hoc: Bonferroni test) tests. Chi-square (post hoc: Bonferroni test) and Fisher Exact tests were used for comparisons between ratios. SPSS 22 program was used for statistical evaluations. $p<0.05$ was considered statistically significant.

RESULTS

The study group consisted of 94 patients, 47 inpatients and 47 outpatients. The mean age was 53.6±15.9 (22-92) years and the number of men and women was equal. Vitamin D levels were <10 ng/ml in 31 patients (33%), 10-29.9 ng/ml in 56 patients (59.6%) and ≥30 ng/ml in 7 patients (7.4%).

Vitamin D levels were found to be normal in only 7 of 94 patients who were followed up in our hospital due to COVID-19. The patients with vitamin D levels ≥30 ng/ml was significantly lower than the patients with vitamin D levels <10 ng/ml and 10-29.9 ng/ml ($p<0.01$ for each).

When the patients were classified according to their vitamin D levels, gender and age distributions were homogeneous ($p=0.100$, $p=0.532$). Inpatient follow-up, high ferritin and D-dimer levels, and poor prognostic factors were found to be significantly higher in patients with low vitamin D levels ($p<0.05$). Apart from these, no significant difference was found between vitamin D levels in terms of radiological involvement, oxygen demand, high CRP, and low lymphocyte count ($p>0.05$). Sociodemographic, clinical characteristics and laboratory results of the patients according to their vitamin D levels were shown in Table 1.

Table 1. Comparison of sociodemographic, clinical and laboratory results of patients according to vitamin D levels

		Experimental groups according to vitamin D levels								p
		<10		10-29.9		≥30		Total		
		n	%	n	%	n	%	n	%	
Gender	**Female**	20	64.5	23	41.1	4	57.1	47	50	0.100
	Male	11	35.5	33	58.9	3	42.9	47	50	
	Total	31	100	56	100	7	100	94	100	
Age*		56.2±17.4 (23-92)		52.1±15.9 (22-86)		53.9±7.5 (44-68)		53.6±15.9 (22-92)		0.532
Clinical status	**Outpatient**	9	29.0	31	55.4	7	100	47	50	**0.001**
	Inpatient	22	71.0	25	44.6	0	0	47	50	
	Total	31	100	56	100	7	100	94	100	
CRP (mg/L)	**0-0.5**	5	16.1	14	25.0	4	57.1	23	24.5	0.074
	>0.5	26	83.9	42	75.0	3	42.9	71	75.5	
	Total	31	100	56	100	7	100	94	100	
Ferritin (ng/ml)	**<20**	1	4.2	2	4.3	1	16.7	4	5.3	**0.003**
	Normal	4	16.7	17	37.0	5	83.3	26	34.2	
	High	19	79.2	27	58.7	0	0	46	60.5	
	Total	24	100	46	100	6	100	76	100	
Lymphocyte count /mm3	**<1000**	17	54.8	30	53.6	3	42.9	50	53.2	0.938
	1000-3700	14	45.2	25	44.6	4	57.1	43	45.7	
	>3700	0	0	1	1.8	0	0	1	1.1	
	Total	31	100	56	100	7	100	94	100	
D-dimer (µg/mL)	**0-0.5**	9	30	31	56.4	6	100	46	50.5	**0.002**
	>0.5	21	70	24	43.6	0	0	45	49.5	
	Total	30	100	55	100	6	100	91	100	
Radiological involvement	**Yes**	21	67.7	40	71.4	2	28.6	63	67.0	0.087
	No	10	32.3	16	28.6	5	71.4	31	33.0	
	Total	31	100	56	100	7	100	94	100	
Oxygen demand	**Yes**	14	45.2	18	32.1	0	0	32	34.0	0.060
	No	17	54.8	38	67.9	7	100	62	66.0	
	Total	31	100	56	100	7	100	94	100	
Presence of at least one of the poor prognostic factors	**Yes**	21	67.7	31	55.4	1	14.3	53	56.4	**0.036**
	No	10	32.3	25	44.6	6	85.7	41	43.6	
	Total	31	100	56	100	7	100	94	100	

*mean±standard deviation (minimum-maximum)

While 22 of the patients (71%) with vitamin D levels <10 ng/ml and 25 of the patients (44.6%) with vitamin D levels between 10-29.9 ng/ml were hospitalized, there was no inpatient treatment among the patients with vitamin D levels ≥30 ng/ml. In Figure 1, the clinical situation of the patients according to their vitamin D levels were indicated.

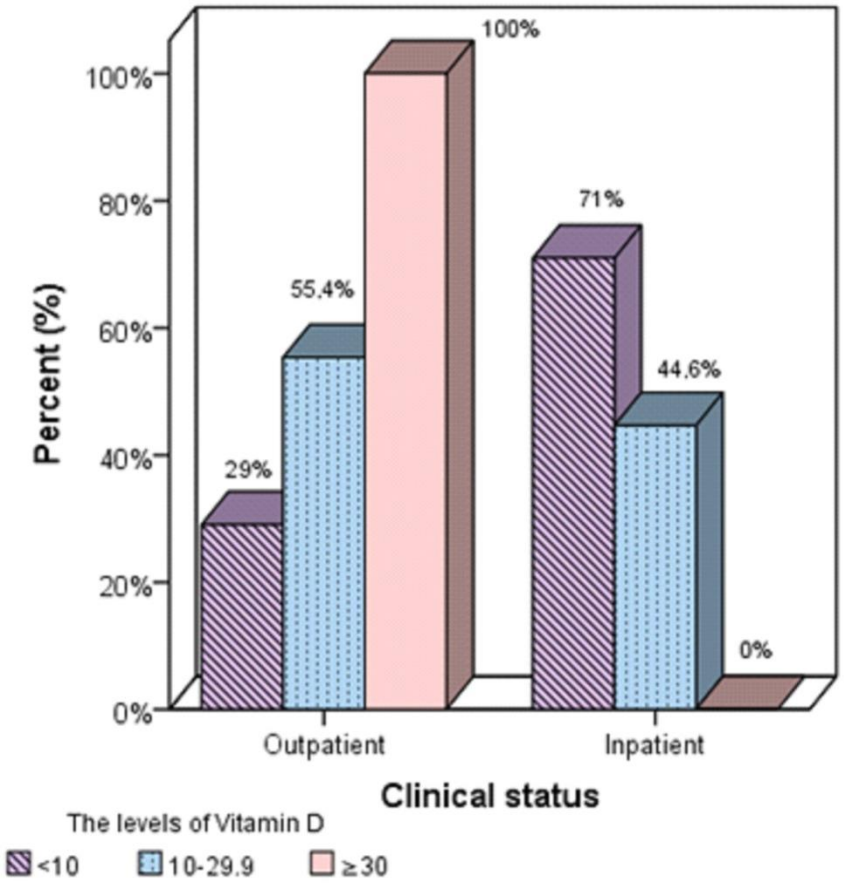

Figure 1. Distribution of clinical situations according to vitamin D levels

The proportion of inpatient (71%) with vitamin D levels <10 ng/ml was significantly higher than that of patients (0%) with vitamin D levels ≥30 ng/ml. In addition, the proportion of outpatients (29%) with vitamin D levels <10 ng/ml was significantly lower than that of those (100%) with vitamin D levels ≥30 ng/ml. The proportions of patients with poor prognosis markers with vitamin D levels <10 ng/ml (67.7%) and 10-29.9 ng/ml (55.4%) were significantly higher than those with vitamin D levels ≥30 ng/ml (14.3%) ($p<0.05$).

The distribution of the patients in terms of the presence of co-morbidity according to their clinical status was given in Table 2. There was a significant difference in the presence of co-morbidity according to clinical status ($p<0.05$). The incidence of co-morbidity in inpatients was 63.8% (n=30), while it was 34% (n=16) in outpatients. Accordingly, the rate of co-morbidity in inpatients was significantly higher than in outpatients ($p<0.05$).

Table 2. The presence of co-morbidity and the effect of vitamin D levels on clinical status

Presence of co-morbidity	25(OH) Vitamin D level (ng/ml)	Clinical status						p
		Outpatient		Inpatient		Total		
		n	%	n	%	n	%	
Yes	**<10**	4	25.0	18	60	22	47.8	**0.039**
	10-29.9	11	68.8	12	40	23	50	
	≥30	1	6.3	0	0	1	2.2	
	Total	16	100	30	100	46	100	
No	**<10**	5	16.1	4	23.5	9	18.8	0.153
	10-29.9	20	64.5	13	76.5	33	68.8	
	≥30	6	19.4	0	0	6	12.5	
	Total	31	100	17	100	48	100	

The presence of co-morbidity, vitamin D levels, and distribution of clinical status of the patients were presented in Table 3. While a significant difference was found in vitamin D levels in patients with co-morbidity according to clinical status ($p<0.05$), it was not observed in patients without comorbidity ($p>0.05$). While vitamin D levels were <10 ng/ml in 60% of the inpatients with co-morbidity, the rate of outpatients was 25%, and the rate of inpatients with related characteristics was significantly higher ($p<0.05$).

Table 3. Comparison of disease outcome, presence of co-morbidity and vitamin D levels

				Groups according to vitamin D levels								p
				<10 ng/ml		10-29.9 ng/ml		≥30 ng/ml		Total		
				n	%	n	%	n	%	n	%	
Co-morbidity	Yes	Disease outcome	Death	8	36.4	2	8.7	0	0.0	10	21.7	0.057
			Healing	14	63.6	21	91.3	1	100	36	78.3	
			Total	22	100	23	100	1	100	46	100	
	No		Death	0	0.0	2	6.1	0	0.0	2	4.2	0.999
			Healing	9	100	31	93.9	6	100	46	95.8	
			Total	9	100	33	100	6	100	48	100	

Vitamin D levels were <10 ng/ml in 4 (23.5%) of 17 inpatients and without co-morbidity, and 10-29.9 ng/ml in 13 (76.5%). Accordingly, vitamin D levels were deficient or insufficient in all inpatients who did not have any co-morbidities.

Of 94 patients, 82 (87%) were cured and 12 (13%) died. Eight (66.7%) of the 12 patients who died had vitamin D levels <10 ng/ml, while 4 (33.3%) had a vitamin D levels 10-29.9 ng/ml. There was no death in patients with a vitamin D levels ≥30 ng/ml. There was no difference between the rates of those with vitamin D levels <10 ng/ml and those with 10-29.9 ng/ml levels ($p=0.248$). Two of the patients who died without co-morbidities had vitamin D deficiency.

DISCUSSION

Vitamin D, which has been thought to be related to bone health for many years, has been accepted as a vitamin and even a hormone that is effective in many diseases such as immune system, cell renewal, course of infections, allergies, autoimmune diseases. Although there are many reasons for this, the most basic of them is that people spend less time outdoors and use high protection factor creams while sunbathing. In addition, another reason is that vitamin D is low in animal foods, which are our main source of vitamin D. This is because animals are mostly kept in closed areas instead of pastures (13). People also consume meat, eggs and dairy products that are low in vitamin D from these sunlight-deprived animals. For these reasons, vitamin D deficiency has become common in societies.

In recent years, there is evidence that vitamin D deficiency is closely related to the severity of infections. It has been reported that vitamin D has positive effects on the strength of physical barriers, which are the foundations of infection immunity, and on the development of natural and acquired immune response (14). Many studies have been conducted which proved that over time Vitamin D did show improvement in the survival rate. Vitamin D has many mechanisms by which it reduces the risk of microbial infection and death (15). A recent review regarding the role of vitamin D in reducing the risk of the common cold grouped those mechanisms into three categories: physical barrier, cellular natural immunity, and adaptive immunity (16). In this study, we determined the effect of vitamin d deficiency on the severity of the clinical condition in COVID-19 patients. In our study, only 7 of the inpatient and outpatient COVID-19 patients had normal vitamin D levels. All inpatients had vitamin D deficiency/insufficiency. Vitamin D levels were low in all patients who died and were inpatient, with or without co-morbidity. To our best knowledge, COVID-19 is more serious in people with co-morbidities. In our study, we found that all inpatients had vitamin D deficiency/insufficiency, although they did not have co-morbidity.

Severe COVID-19 is characterized by an over-response of the immune system called as a cytokine storm. Infection is largely limited by the strength of the mucosal barriers and innate immune response in individuals with normal vitamin D levels (17). Moreover, serious infections do not develop in these people. Several studies demonstrated the role of vitamin D in reducing the risk of acute viral respiratory tract infections and pneumonia (18). Additionally, it was reported that high levels of vitamin D can reduce pulmonary fibrosis by reducing interleukin 1 beta levels of pro-inflammatory cytokines produced by pulmonary fibroblast cells in a mouse model of bleomycin-induced lung fibrosis (19). These include direct inhibition with viral replication or with anti-inflammatory or immunomodulatory ways. Petrelli and colleagues have associated the risk of COVID-19 infection with patients with low vitamin D levels resulting in a worse prognosis and higher mortality rate compared to patients with vitamin D levels in the normal range (20). Therefore, vitamin D levels might be associated with the course of COVID-19 disease.

CONCLUSIONS

In line with our findings, vitamin D deficiency is associated with severe COVID-19. Many similar studies have been found in the literature. It is very important for people to keep their vitamin D levels within normal levels by using vitamin D before they get sick.

REFERENCES

1. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. http://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020. Accessed 12 Feb 2020
2. Yu P, Zhu J, Zhang Z, Han Y. A Familial Cluster of Infection Associated with the 2019 Novel Coronavirus Indicating Possible Person-to-Person Transmission During the Incubation Period. J Infect Dis. 2020;221(11):1757-61.
3. Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermatoendocrinol. 2013;5(1):51-108.
4. Christakos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ. Vitamin D: metabolism. Endocrinol Metab Clin North Am. 2010;39(2):243-53.
5. Alshishtawy MM. Vitamin D Deficiency: This clandestine endemic disease is veiled no more. Sultan Qaboos Univ Med J. 2012;12(2):140-52.
6. Hewison M. Vitamin D and innate and adaptive immunity. Vitam Horm. 2011;86:23-62.
7. Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. J Clin Virol. 2011;50(3):194-200.
8. Munshi R, Hussein MH, Toraih EA, Elshazli RM, Jardak C, Sultana N, et al. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. J Med Virol. 2021;93(2):733-40.
9. Merzon E, Tworowski D, Gorohovski A, Vinker S, Golan Cohen A, Green I, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS J. 2020;287(17):3693-702.
10. Kumar R, Rathi H, Haq A, Wimalawansa SJ, Sharma A. Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19. Virus Res. 2021;292:198235.
11. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America Expert Consensus Document on Reporting Chest CT Findings Related to COVID-19: Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA. Radiol Cardiothorac Imaging. 2020;2(2):e200152.
12. Smith DL, Grenier JP, Batte C, Spieler B. A Characteristic Chest Radiographic Pattern in the Setting of the COVID-19 Pandemic. Radiol Cardiothorac Imaging. 2020;2(5):e200280.
13. Schmid A, Walther B. Natural vitamin D content in animal products. Adv Nutr. 2013;4(4):453-62.
14. Rondanelli M, Miccono A, Lamburghini S, Avanzato I, Riva A, Allegrini P, et al. Self-Care for Common Colds: The Pivotal Role of Vitamin D, Vitamin C, Zinc, and Echinacea in Three Main Immune Interactive Clusters (Physical Barriers, Innate and Adaptive Immunity) Involved during an Episode of Common Colds-Practical Advice on Dosages and on the Time to Take These Nutrients/Botanicals in order to Prevent or Treat Common Colds. Evid Based Complement Alternat Med. 2018;2018:5813095.
15. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020;12(4):988.
16. Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Mol Nutr Food Res. 2011;55(1):96-108.
17. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health. 2020;13(10):1373-1380.
18. Kim JS, Lee JY, Yang JW, Lee KH, Effenberger M, Szpirt W, et al. Immunopathogenesis and treatment of cytokine storm in COVID-19. Theranostics. 2021;11(1):316-329.
19. Tsujino I, Ushikoshi-Nakayama R, Yamazaki T, Matsumoto N, Saito I. Pulmonary activation of vitamin D3 and preventive effect against interstitial pneumonia. J Clin Bioc hem Nutr. 2019;65(3):245–251.
20. Pereira M, Dantas Damascena A, Galvao Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2022;62(5):1308-1316.