The Effect of Active Vitamin D on Coronavirus

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Abstract. Coronaviruses, especially Beta coronaviruses (β)is a threat to humans since it spreads easily. Although we are yet to find a cure to COVID-19, there are various approaches to prevent its spread, including UV and heat inactivation. However, recently scholars have identified an increased relationship between vitamin D-deficiency and the severe COVID-19, making it a feasible intervention to treat or prevent COVID-19. We can obtain vitamin D directly through sunlight, diet, or supplementation. Vitamin D, especially vitamin D_2 and D_3 prevents COVID-19 by enhancing anti-inflammatory and eradicating pro-inflammatory cytokines and acting as an antiviral by augmenting B-defensin and antimicrobial peptides cathelicidin, declining viral replication. People with vitamin D deficiency are more susceptible to SARS-CoV-2 than normal peopole. Vitamin D is safe and has limited adverse events because although it is a fat-soluble vitamin, humans rarely experience vitamin D overdose, including vitamin D overdoses due to sunlight.

Keywords: Vitamin D Deficiency; UV; COVID-19; Coronavirus.

1. The Effect of Active Vitamin D on Coronavirus

Following the outbreaks of SARS in 2022 and MERS in 2012, COVID-19 is the 3rd 21st-century coronavirus (CoV)-related pandemic that emerged in humans and a red-level alert was assert by the World Health Organization (WHO). It is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in Wuhan, China, and was transmitted to other parts of the world. The WHO declared that COVID-19 as a novel pandemic on February 11, 2020, with variation in clinical characteristics, including 15.7 % patients had a severe illness, and 17.9 % infections were mild (Almehmadi et al., 2021). COVID-19 exhibits an early immune suppression, followed by an anomalously activated immune response, including the cytokine storm. The infection triggers severe consequences, including systemic inflammatory response syndrome and acute respiratory distress syndrome (Almehmadi et al., 2021). All infection incidents, recent epidemics, and the COVID-19 pandemic confirm that CoVs threaten humans and the economy continuously since they spread easily, emerge unexpectedly, and cause catastrophic consequences. We do not have a consensus on the treatment for coronavirus infections, including COVID-19. However, we have several vaccines, such as Johnson & Johnson's Janssen, along with several clinical trials for coronavirus medications on various immune-impacting options, such as vitamin D(V_D). $V_{D\ 2}$ and $V_{D\ 3}$ has been linked with various maladies, including diabetes, osteoporosis, inflammation, immune dysregulation, hypertension, certain malignancies, cognitive decline, and cardiovascular disease (Hribar et al., 2020). While different disinfectants can inactivate coronavirus, active vitamin D has been associated with decreased coronavirus infection.

2. The Coronavirus Particle

The new coronavirus or pneumonia virus is a highly pathogenic and transmissible viral infection. Coronavirus can be categorized into four genera: *Alphacoronaviruses* (α)*, Deltacoronaviruses* (δ), *Betacoronaviruses* (β)*,* and *Gammacoronaviruses* (γ), and these viruses are detected in various species, including humans (Chu et al., 2020). The new coronavirus is a β-CoVs and is genetically identical to the bat's *Sarbecovirus*. Like other coronaviruses, β-CoVs is enveloped, positive-sense, non-segmented, single-stranded RNA virus, which bearing the largest known viral RNA genome (Figure 1) (Li et al., 2020; Malik, 2020). The virion comprises a nucleocapsid encompassing phosphorylated N protein and genomic RNA. The N protein is buried in phospholipid bilayers with two forms of spike proteins: the hemagglutinin-esterase, present in some CoVs, and the S trimmer

was found in all CoVs (Li et al., 2020). The E protein and M protein are situated among the S proteins in the virus envelope.

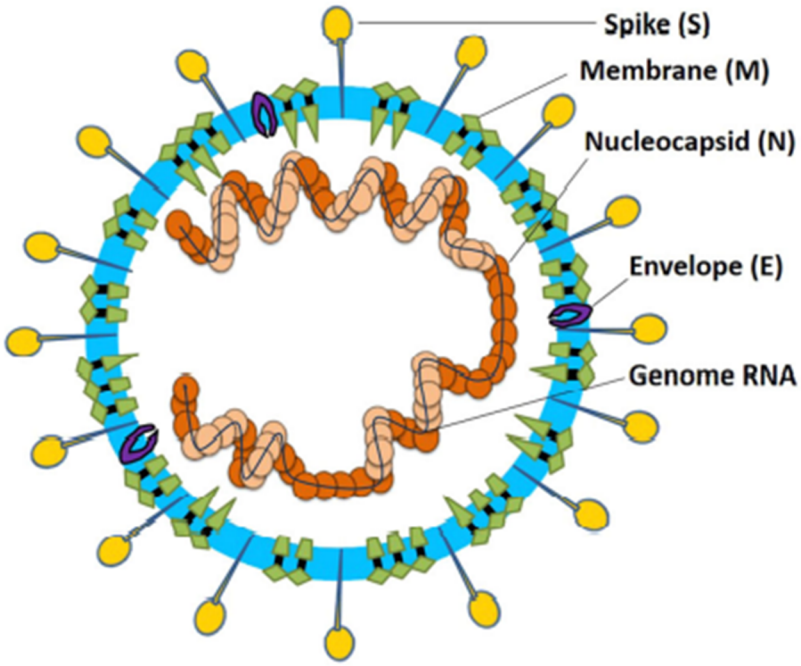

Figure 1. Coronavirus Particle (Li et al., 2020)

3. Disinfecting CoVs

The effective method of inactivating the coronavirus depends on the biological characteristics of the coronavirus. Coronavirus is sensitive to ultraviolet (UV) light and heat. Heat inactivation is common; however, UV irradiation is preferred since it inactivates coronaviruses by modifying their nucleic acid structure. Inactivating SARS-CoV-2 using UV allows safe virus usage within the laboratory and deters the likelihood of laboratory-acquired infections (Patterson et al., 2020). UV radiation disinfection can be performed robotically and used to disinfect liquids, air, surfaces, and rooms, and it is energy-efficient. According to Heßling et al. (2020), UVC has the strongest antiviral properties, and for RNA viruses, such as CoVs, the leading inactivation mechanism is shown in figure 2.

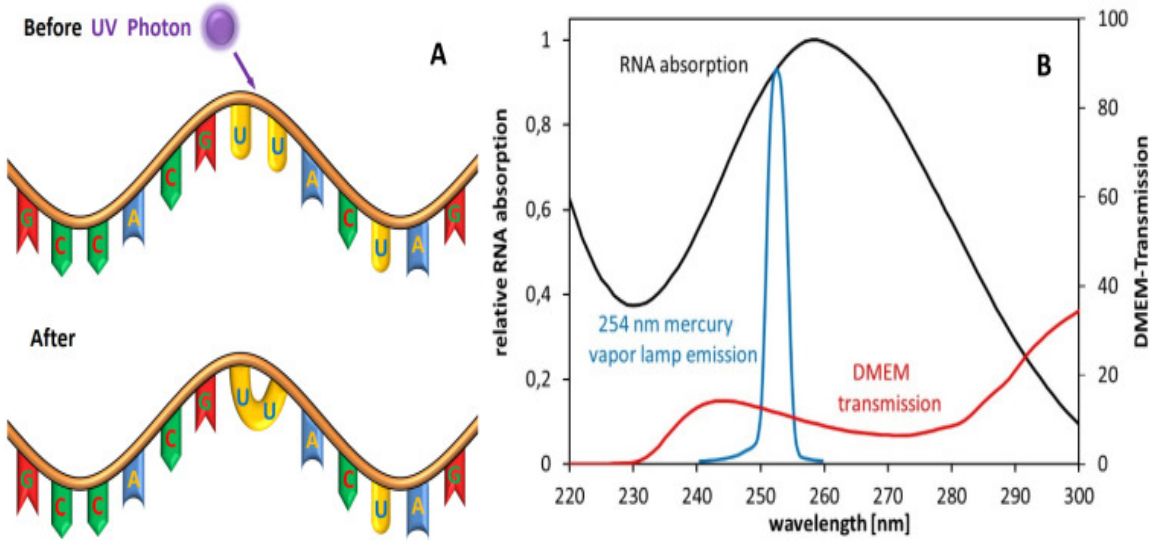

Figure 2. UV-RNA-Damaging Mechanism and Relative Absorbtion Spectra of RNA (Heßling et al., 2020)

As illustrated in figure 2, RNA absorbs UV radiation, leading to the formulation of pyrimidine dimers, such as uracil dimers, and the strongest peak UV emission is approximately 254 nm, near the RNA absorption maximum at approximately 260 nm. Despite the use of heat and UV radiation, researchers are finding other ways to decrease the death toll and control the risks of COVID-19 infections. However, one challenge in preventing CoVs, such as the SARS-CoV-2, is the absence of evidence illustrating effective drug measures. V_D has been initially reported to encompass a functional role in treating and preventing viral infections, including SARS-CoV-2.

4. V_D: Special Consideration in COVID-19 Patients

V_D levels in adults and children are associated with asthma and health. It stimulates intestinal phosphate, calcium, and magnesium absorption and has diverse biological effects. As a result, V_D is interlinked with the maintenance of phosphate and calcium balance and parathyroid hormone (PTH) action. V_D can be intaked into our body in various ways: supplementation, diet, or sunlight. In our skin, UVB rays activate V_D precursor 7-dehydrocholesterol when it becomes $V_{D\ 3}$ (Hribar et al., 2020). $V_{D\ 2}$ is made of ergosterol in plants or yeast by ultraviolet irradiation. People can obtain $V_{D\ 2}$ and $V_{D\ 3}$ directly from fatty fish, supplementation, fortified milk, juices, dairy products, and cereals in the diet. Our liver then converts $V_{D\ 2}$ and $V_{D\ 3}$ to 25-hydroxyvitamin D (25 (OH) D_3) that joint to vitamin D binding proteins (DBPs) in serum. Hribar et al. (2020) indicate that 25-hydroxyvitamin D25 (OH) D_3 in serum is the optimal marker for establishing V_D deficiency, and this type of V_D is activated in kidneys by 25-hydroxyvitamin D-1-alpha-hydroxylase (1-OHase, induced by PTH), becoming 1,25-dihydroxy V_D (1,25(OH)2D, Calcitriol). Calcitriol is a pluripotent hormone and an essential adaptive and innate immunity modulator. Often, older adults exhibit low level of V_D, possibly due to declined mobility and the duration outside in open spaces or sunlight, decreased rates of synthesis of V_D in their skin, amplified adiposity, decreased V_D absorption in the gut, and lessened appetite.

V_D deficiency is an important health problem that increases people's vulnerability to coronavirus infections, including COVID-19. Approximately one billion people have V_D deficiency globally (Almehmadi et al., 2021; Nimavat et al., 2021). In winter, incidents of influenza increase due to decreased access to vitamin D via sunlight. Particularly, the influenza pandemic in 1819 reached its peak in January, and the new crown pneumonia, or COVID-19, reached its peak in January. According to Nimavat et al. (2021), if optimum V_D levels are achieved, it lessens viral infections, such as influenza, Dengue, Hepatitis B and C, HIV, and pneumonia. Maintaining a healthy respiratory system requires effectively removing pathogenic microorganisms and controlling the body's inflammatory levels. V_D can activate the way to resist microorganisms, to enhance the respiratory tract's resistance to infection, and the respiratory tract's ability to resist infection. V_D exerts important anti-inflammatory and antiviral effects through its immunoregulatory rules through V_D receptors on several immunological cells.

V_D could decrease the risk of SARS-CoC-2 infection through various ways. Firstly, it can enhance anti-inflammatory and diminish pro-inflammatory cytokines including IL-6, TNF-α, and IFN-γ, which would trigger lung injury and pneumonia. Secondly, V_D acts as an antiviral by amplifying B-defensin and antimicrobial peptides cathelicidin, decreasing viral replication (Almehmadi et al., 2021; Darif et al., 2021). Those pro-inflammatory cytokines are relative to severe outcomes in coronavirus infections, including COVID-19. As illustrated in figure 3, the binding of S-protein to ACE2 protein on the membrane of epithelial cells on the gut or respiratory tract triggers cytokine release or a pro-inflammatory cascade. The uncontrolled generation of pro-inflammatory cytokines is a kind of common feature in severe COVID-19 patients, which is also called cytokine release syndrome. V_D comprises immuno-modulatory features, including restraining the release of pro-inflammatory cytokines, and attenuates lipopolysaccharides-generated acute lung injury in murine model through blocking the angioprotein -2-Tie-2 and the renin-angiotensin pathway (Pinzon & Pradana, 2020). By diminishing the pro-inflammatory cytokines, V_D prevents several consequences in COVID-19

patients, including acute lung injuries, microbiota alteration, cellular damage, a reduction in regulatory T cells, and severe lymphopenia (figure 3).

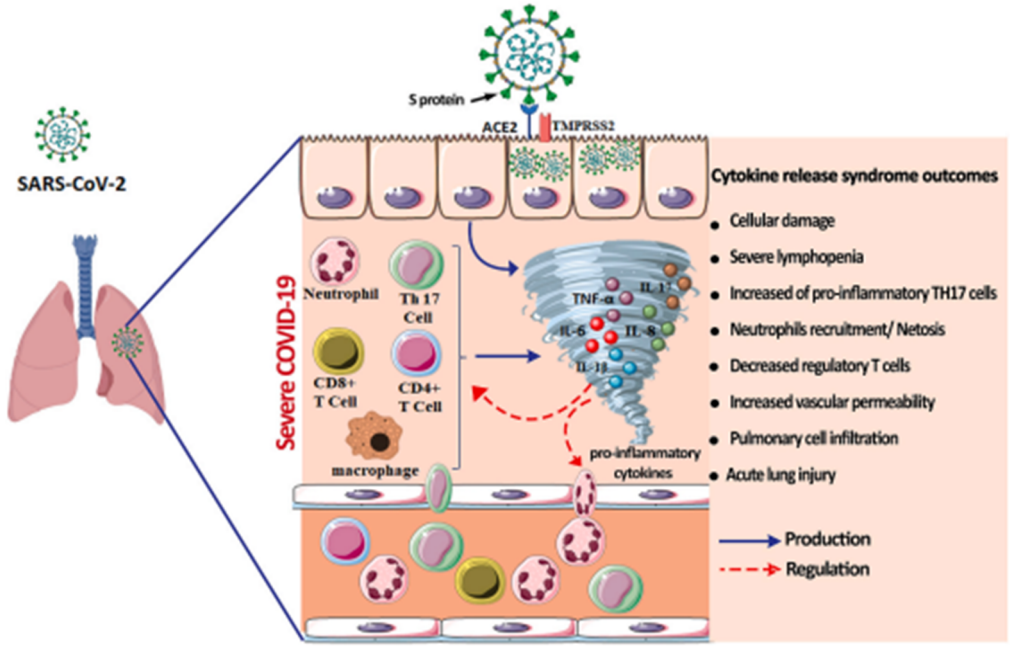

Figure 3. The Cytokine and Clinical Outcomes in COVID-19 (Darif et al., 2021)

Furthermore, severe COVID-19 infection is linked to an extended, amplified IFN gamma-producing Th1 and high levels of activated complement responses. Excessive IFN gamma and complement are drivers of tissue injury or damage. SARS-CoVs-infected respiratory epithelia cells process and express complement. According to Gibbons et al. (2022), "C3b binds the CD46 receptor on CD4 + T cells to drive TH1 differentiation normally followed by their shutdown." Th1 cells produce IL10 to control inflammation. Scholars have identified a paracrine/autocrine V_D loop that allows Th1 cells to respond and activate V_D as a segment of the cellular program to s enhance IL10 and shutdown IFN gamma. This finding validates that adding or including V_D in immunomodulatory agents may treat patients with coronavirus infections, including COVID-19 (Gibbons et al., 2022). Thus, V_D can be associated with the SARS-CoVs severity, infection, and survival of COVID-19 patients.

The evidences from various research confirms that frequent intake of $V_{D\ 2}$ or $V_{D\ 3}$ is protective and safe against acute respiratory tract infections, including SARS-CoV-2, especially in patients with V_D deficiency. In their study, Almehmadi et al. (2021) observed that 49% of the COVID-19 patients (81/166) had vitamin D deficiency, while 21% had insufficient V_D (37/166), totaling to 78% insufficiency or deficiency in V_D (118/166) (Table 1). They discovered that V_D deficiency included older adult patients

Table 1. Comparison Between COVID-19 Patients Based on Their Demographic Data (Almehmadi et al., 2021)

Parameter	Deficiency (n=8)	Insufficiency (n=48)	Sufficiency (n=37)	P-value
Age (years) Mean ± SD	61 ± 15	56±15	54±16	0.06
Sex				
Female	24 (30%)	15 (31%)	19 (51%)	-
Male	57 (70%)	33 (69%)	18 (49%)	0.06

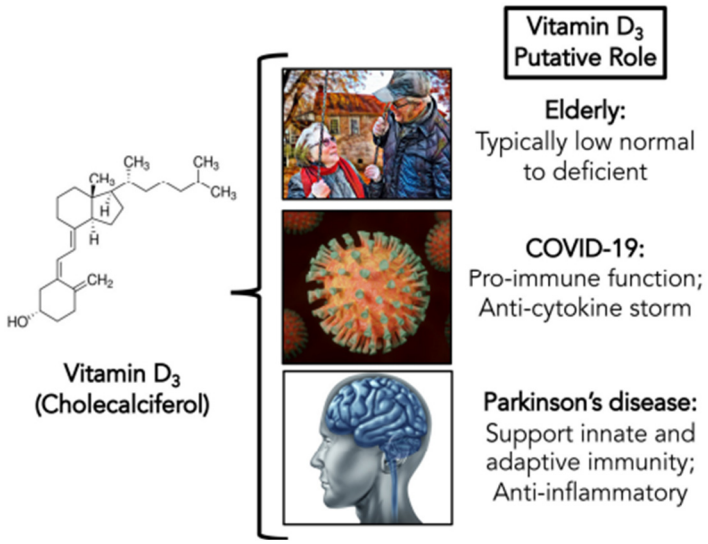

Figure 4. The Possible Roles of V_D supplementation in Older Adults, With Special Consideration to Parkinson's Disease Patients' Risk of Developing COVID-19 (Hribar et al. (2020)

Table 2. Demographic Information on COVID-19 Patients, V_D Deficiency, COVID-19 With V_D Deficiency, and Hospital Population (Katz et al., 2020)

	Odds ratio	95% Wald confidence limits		P value
V_D deficiency vs. no deficiency	4.633	3.713	5.783	< 0.001
V_D deficiency vs. no deficiency	4.583	3.668	5.726	< 0.001
Sex male vs. female	0.935	0.818	1.069	0.3278
V_D deficiency vs. no deficiency	3.757	2.982	4.734	< 0.001
Race black vs. other	3.424	2.837	4.134	< 0.001
Race white vs. other	1.325	1.122	1.565	< 0.001
V_D deficiency vs. no deficiency	5.155	3.974	6.688	< 0.001
Age 18-44 vs. <18	1.15	0.812	1.628	< 0.001
Age 45-64 vs. <18	0.585	0.409	0.838	0.0074
Age >64 vs. <18	0.439	0.305	0.631	< 0.001
V_D deficiency vs. no deficiency	3.64	2.911	4.55	< 0.001
PD vs. no PD	2.976	1.679	5.275	0.0002
V_D deficiency vs. no deficiency	3.764	3.025	4.685	< 0.001
Caries vs. no caries	2.612	1.892	3.605	< 0.001
V_D deficiency vs. no deficiency	3.918	3.157	4.862	< 0.001
PA vs. no PA	3.044	1.928	4.805	< 0.001
V_D deficiency vs. no deficiency	2.266	1.787	2.872	< 0.001
Obesity vs. no obesity	4.884	4.165	5.728	< 0.001
V_D deficiency vs. no deficiency	3.28	2.591	4.151	< 0.001
Diabetes vs. no diabetes	2.926	2.404	3.561	< 0.001
V_D deficiency vs. no deficiency	4.461	3.554	5.599	< 0.001
Malabsorption vs. no malabsorption	1.267	0.595	2.7	0.5389

COVID-19, coronavirus disease 2019; PD, periodontal disease. PA periapical abscesses

According to Hribar et al. (2020), older adults show low V_D levels and are most vulnerable to COVID-19 (Figure 4). Older adults with Parkinson's disease have been independently observed to have lower V_D amounts than healthy individuals. This aspect places older adults in a unique position in which their vulnerability to developing COVID-19 infection is augmented than other populace. Besides, Hribar et al. (2020) noted that V_D supplementation is advantageous in enhancing non-motor and motor symptoms of Parkinson's disease and lessening the risk of falls and associated fractures. In a similar study, Katz et al. (2021) confirm that patients with V_D deficiency are 4.633 times more likely to be infected by the COVID-19 virus than those without V_D deficiency (Table 2). In this research, from 98784, 31950 people had V_D deficiency, 887 had COVID-19, and 87 patients had COVID-19 and V_D deficiency. As demonstrated in Table 2, the subgroup of 87 patients had 98% adults, 88% black or other non-white people, and 73.3% males (Katz et al., 2021). Interestingly after adjusting for age groups, Katz et al. (2021) observed that individuals with V_D deficiency are five times more likely to be infected with COVID-19 than those with sufficient V_D (Table 2). Patients with low V_D status are more likely to test positive for COVID-19 than those without it. In Table 3, Meltzer et al. (2020) exhibit a multivariable linear model for testing COVID-19 positive. The deficient V_D group is 21.6 % more likely to test positive for COVID-19, while those with sufficient V_D are 12.2 % likely to test positive (Table 3). These studies amplify the consideration of whether V_D supplementation reduces COVID-19 risk.

5. V_D Supplementation for COVID-19 Prevention: Adverse Events and Safety

Since V_D deficiency has been illustrated to augment the risk of severe respiratory infections potentially, some scholars suggest V_D supplements for treating and preventing COVID-19. V_D is safe and has limited adverse events. Although it is a fat-soluble vitamin, people rarely experience V_D overdose, including V_D overdoses due to sunlight. According to Hribar et al. (2020), "hypervitaminosis D is almost exclusively related to over-supplementation" (p.4). Scholars postulate that direct synthesis types of $25(OH)D_3$ are less likely to bind to DBPs; hence, oral $V_{D\ 2}$ and $V_{D\ 3}$ supplementation are the preferred options for augmenting V_D. The United States (US) Institute of Medicine recommends a successive everyday V_D limit of 4000 IU/day; yet, safe everyday supplementation may reach about 7,500 -10,000 IU/day (Hribar et al., 2020). People may consume large bolus doses in dire clinical situations; however, they should do it under the supervision of a doctor because the risk of V_D overdose and associated adverse events augment with these approaches.

Scholars investigating V_D 's influence on the immune response recommend a serum level of 40-60 ng/mL $25(OH)D_3$ for respiratory infection treatment/prevention. Interestingly, as Wimalawansa (2022), people do not experience adverse events or safety issues of vitamin D_3 supplementation until the serum concentrations of $25(OH)D_3$ surpass 60 ng/mL (150 nmol/L). V_D overdose's most common side effects include nausea, weakness, vomiting, poor appetite, weight loss, or constipation. Excessive $V_{D\ 3}$ supplementation can amplify calcium, resulting in gastrointestinal upset, fatigue, confusion, arrhythmias, kidney damage, nephrolithiasis, and disorientation. Despite these adverse events and risks, V_D hypervitaminosis is rare. It would need excessive $V_{D\ 3}$ supplementation daily for a long period, making it a safe supplement for several people, including older adults, at increased risk of SARS-CoV-2 infection.

Since V_D deficiency has been illustrated to amplify the risk of severe respiratory infections, we can use V_D supplements to treat and prevent the new coronavirus and COVID-19 infections. Individuals with low V_D are 4.633 times to test positive for COVID-19 than people with sufficient V_D. We can obtain V_D directly from the sun or diet. Older adults, especially those with chronic ailments such as Parkinson's disease and low V_D, are more susceptible to COVID-19 than others. This group exhibit low V_D due to limited movement and sunlight exposure, confirming that V_D can inactivate coronaviruses, including SARS-CoV-2 and COVID-19. V_D prevents COVID-19 by enhancing anti-inflammatory and eliminating pro-inflammatory cytokines (TNF-α, IL-6, and IFN-γ)

and acting as an antiviral by augmenting B-defensin and antimicrobial peptides cathelicidin, declining viral replication.

Table 3. Multivariable Association of V_D Deficiency and Treatment Testing Positive for COVID-19 in 489 Patients (Meltzer et al., 2020)

Characteristic	No (%)	Relative risk (95% CI)	P value
Age			
<50	260 (53)	1.05 (1.01-1.09)	0.02
≥50	229 (47)	1.02 (1.00-1.05)	0.06
Sex			
Male	123 (25)	1 [Reference]	
Female	366 (75)	0.87 (0.52-1.44)	0.58
Race			
White	158 (32)	1 [Reference]	
Other than White	331 (68)	2.54 (1.26-5.12)	0.009
Ethnicity			
Non-Hispanic	448 (92)	1 [Reference]	
Hispanic	41 (8)	0.29 (0.04-2.01)	0.21
Employee status, UCM employee			
No	328 (67)	1 [Reference]	
Yes	161 (33)	0.93 (0.52-1.64)	0.79
Most recent V_D			
Likely deficient	124 (25)	1.77 (1.12-2.81)	0.02
Uncertain deficiency	48 (10)	1.10 (0.49-2.43)	0.82
Uncertain deficiency	30 (5)	1.09 (0.43-2.82)	0.85
Likely sufficient	287 (59)	1	
Comorbidity indicators			
Hypertension	261 (53)	1.08 (0.60-1.97)	0.79
Diabetes	137 (28)	0.78 (0.49-1.26)	0.31
Chronic pulmonary disease	117 (24)	0.91 (0.55-1.52)	0.73
Pulmonary circulation disorders	20 (4)	0.64 (0.23-1.79)	0.40
Depression	119 (24)	1.22 (0.74-2.02)	0.44
Chronic kidney disease	116 (24)	0.80 (0.49-1.32)	0.39
Liver disease	56 (11)	0.99 (0.47-2.08)	0.98
Comorbidities with immunosuppression	105 (21)	0.39 (0.20-0.76)	0.005
BMI, mean	29.8	1.02 (0.996-1.048)	0.10
	NA	NA	0.87
	NA	NA	0.89

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