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Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence

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Abstract

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Importance: Vitamin D treatment has been found to decrease incidence of viral respiratory tract infection, especially in vitamin D deficiency. It is unknown whether COVID-19 incidence is associated with vitamin D deficiency and treatment.

Objective: To examine whether vitamin D deficiency and treatment are associated with testing positive for COVID-19.

Design: Retrospective cohort study

Setting: University of Chicago Medicine

Participants: Patients tested for COVID-19 from 3/3/2020-4/10/2020. Vitamin D deficiency was defined by the most recent 25-hydroxycholecalciferol <20ng/ml or 1,25-dihydroxycholecalciferol <18pg/ml within 1 year before COVID-19 testing. Treatment was defined by the most recent vitamin D type and dose, and treatment changes between the time of the most recent vitamin D level and time of COVID-19 testing. Vitamin D deficiency and treatment changes were combined to categorize vitamin D status at the time of COVID-19 testing as likely deficient(last-level-deficient/treatment-not-increased), likely sufficient(last-level-not-deficient/treatment-not-decreased), or uncertain deficiency(last-level-deficient/treatment-increased or last-level-not-deficient/treatment-decreased).

Main Outcomes and Measures: The main outcome was testing positive for COVID-19. Multivariable analysis tested whether the most recent vitamin D level and treatment changes after that level were associated with testing positive for COVID-19 controlling for demographic and comorbidity indicators. Bivariate analyses of associations of treatment with vitamin D deficiency and COVID-19 were performed.

Results: Among 4,314 patients tested for COVID-19, 499 had a vitamin D level in the year before testing. Vitamin D status at the time of COVID-19 testing was categorized as likely deficient for 127(25%) patients, likely sufficient for 291(58%) patients, and uncertain for 81(16%) patients. In multivariate analysis, testing positive for COVID-19 was associated with increasing age(RR(age<50)=1.05,p<0.021;RR(age≥50)=1.02,p<0.064)), non-white race(RR=2.54,p<0.01) and being likely vitamin D deficient (deficient/treatment-not-increased:RR=1.77,p<0.02) as compared to likely vitamin D sufficient(not-deficient/treatment-not-decreased), with predicted

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COVID-19 rates in the vitamin D deficient group of 21.6%(95%CI[14.0%-29.2%]) versus 12.2%(95%CI[8.9%-15.4%]) in the vitamin D sufficient group. Vitamin D deficiency declined with increasing vitamin D dose, especially of vitamin D3. Vitamin D dose was not significantly associated with testing positive for COVID-19.

Conclusions and Relevance: Vitamin D deficiency that is not sufficiently treated is associated with COVID-19 risk. Testing and treatment for vitamin D deficiency to address COVID-19 warrant aggressive pursuit and study.

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COVID-19, caused by the SARS-CoV-2 coronavirus, often produces severe lower respiratory symptoms and has caused 200,000 deaths worldwide.[1] One challenge in halting this pandemic is the absence of evidence demonstrating effective pharmacologic interventions to prevent COVID-19. Vitamin D has been identified as a potential strategy to prevent or treat COVID-19.[2] Vitamin D treatment has been found to decrease other viral respiratory infections, especially in persons with vitamin D deficiency.[3] Vitamin D deficiency is common, affecting nearly half the US population, with higher rates among persons with darker skin or reduced sun exposure, including persons living in higher latitudes in the winter, nursing home residents, and health care workers.[4] COVID-19 is more prevalent among African-Americans,[5] persons living in northern cities in the late winter,[6] older adults,[7] nursing home residents[8] and health care workers,[9] populations which all have increased risk of vitamin D deficiency.[10,11,12,13] Moreover, COVID-19 is less prevalent in pregnant women and children[14], and in persons living in Japan[15], in whom rates of vitamin D deficiency are lower.[16,17,18] Shelter in place orders to reduce the spread of COVID-19 may also decrease sun exposure, potentially worsening vitamin D levels and providing further rationale for vitamin D supplementation.[19] Given the low risks and low cost of vitamin D treatment, it has been suggested that vitamin D treatment should be rapidly scaled based on existing evidence.[20,] Nevertheless, evidence of whether vitamin D deficiency is associated with COVID-19 infection is lacking and could help establish vitamin D as an evidence-based approach to decrease the burden and potentially the spread of COVID-19.

Using data from the electronic health record at the University of Chicago Medicine (UCM) in Chicago, IL, we examined whether persons tested for COVID-19 were more likely to test positive for COVID-19 if they were vitamin D deficient than if they were not vitamin D deficient. Because patients may have had changes in their vitamin D treatment after the time of their most recent vitamin D level prior to COVID-19 testing, we combined data on patients' last vitamin D level before COVID-19 testing and changes in their treatment after that vitamin D level to construct a measure of whether each patient was expected to have a deficient, sufficient, or uncertain vitamin D level at the time they were tested for COVID-19. We also tested whether the type and dosage of vitamin D supplementation was associated with vitamin D levels and COVID-19.

Methods

Study Design and Oversight

The underlying motivation for our analysis is that if vitamin D deficiency increases the risk of COVID-19, then persons with vitamin D deficiency tested for COVID-19 should be more likely to test positive than persons being tested who are not vitamin D deficient. Based on this hypothesis, we obtained IRB approval for a preliminary bivariate analysis examining whether patients tested for COVID-19 at UCM were more likely to test positive for COVID-19 if they had

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a documented deficient level of vitamin D in the past 2 years compared to patients with non-deficient vitamin D levels. This preliminary analysis demonstrated an increased rate of testing positive for COVID-19 among persons with vitamin D deficiency and suggested the importance of examining data on vitamin D treatments after the time of these test results. Since a large fraction of the persons tested at UCM were UCM health care workers, exploratory analyses were begun to inform UCM internal operations in parallel with IRB submission of this study, which was approved by the University of Chicago Biological Sciences Division IRB.

Participants

We obtained data for all 4,314 persons tested for COVID-19 at UCM from March 3, 2020 to April 10, 2020. We obtained electronic health record data for required demographic, comorbidity, laboratory and medication data, including 25(OH)-vitamin D levels within 2 years before COVID-19 testing. Vitamin D levels and treatments within 14 days of COVID-19 testing were excluded from analyses to avoid possible confounding by potential early manifestations of COVID-19, such as presenting for health care with symptoms that could lead to testing for and treatment of vitamin D deficiency. This resulted in 22 patients being excluded.

Measurements

All variables were defined based on information from the UCM electronic health record, Epic® (Verona, WI). COVID-19 test status was determined by any positive COVID-19 RNA test result. Because of limitations on testing, testing at UCM was focused on persons presenting with potential symptoms of COVID-19 admitted to the hospital or health care workers with COVID-19 symptoms and exposure. The first date of testing positive for COVID-19 was used to determine the testing date for calculating variables defined in relation to the testing date. Patients with a most recent 25(OH)-vitamin D level <20 ng/ml within 1 year of COVID-19 testing were deemed vitamin D deficient. Patients with a most recent vitamin D levels within 1 year ≥20 ng/ml were deemed not vitamin D deficient. Patients treated with calcitriol and with calcitriol levels were classified as vitamin D deficient if the calcitriol levels <18 pg/ml. Vitamin D3 dosing was defined based on most recent daily dose recorded over the past 2 years excluding the 14 days before testing positive: None, 1-1000IU or a multivitamin, 2000IU, ≥3000IU. Indicators for treatment with D2 and calcitriol were also included. To account for possible changes in patients' vitamin D treatment after the time of their last vitamin D level, we combined the data on the last vitamin D level and changes in treatment after that vitamin D level to assign each patient to one of four categories reflecting their likelihood of being vitamin D deficient at the time of COVID-19 testing: 1) deficient/treatment-not-increased (likely deficient), 2) not-deficient/treatment-not-decreased (likely sufficient), and 3) deficient/treatment-increased and 4) not-deficient/treatment-decreased, indicating uncertain

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vitamin D sufficiency. Days from most recent vitamin D level to COVID-19 diagnosis was constructed for sensitivity analysis.

Age, gender, race, Hispanic ethnicity were also obtained and coded as reported in Table 1. BMI and the following ICD-10-CM-based Elixhauser comorbidity clusters[21] potentially related to COVID-19 coded based on all encounters during the period: hypertension, diabetes, chronic pulmonary disease, pulmonary circulation disorders, depression, and immunosuppression. Comorbidity indicators for liver disease and chronic kidney disease were also included because their potential roles in affecting levels of activated vitamin D.

Statistical Analysis

Basic descriptive statistics were reviewed for all variables. Fisher's exact test was used to compare rates of testing positive for persons with last vitamin D levels that were deficient and persons with last levels that were not deficient. A multivariable generalized linear model (GLM) with binomial residuals and log link function[22] was estimated with the covariates noted above. We also tested whether treatment dose/type was associated with vitamin D deficiency and COVID-19. In the bivariate COVID-19 analysis, patients were included if they had a diagnosis of vitamin D deficiency defined by having any deficient vitamin D level or recorded ICD-10-CM code for vitamin D deficiency within 2 years.

Results

Characteristics of the Patients

All 4,314 patients tested for COVID-19 during the study period had a test result. Of these, 499 had a vitamin D level in the year before testing, including 178(36%) with vitamin D deficiency. Four-hundred-twenty-eight(10%) patients tested for COVID-19 had a diagnosis of vitamin D deficiency within 2 years. Table 1 provides descriptive statistics for all patients with a COVID-19 test result and comparisons of demographic and comorbidity indicators, treatments and rates of testing positive for COVID-19 for the cohorts of patients stratified by whether their last vitamin D level was deficient.

Table 1 indicates no significant differences between patients whose last vitamin D level was or was not deficient except that vitamin D deficient patients are more likely to be younger, African American, have deficient vitamin D levels, and receive vitamin D2 and less likely to receive vitamin D3.

Thirty-two of 178(18%) vitamin D deficient patients tested positive for COVID-19 versus 40 of 321(11%) non-deficient patients(p=0.11).

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Supplemental Table 1 repeats these descriptive analyses dividing the sample among the 4 groups combining deficiency status and treatment changes after the last vitamin D level to infer vitamin D status at the time of COVID-19 testing. The results are similar but show some additional differences in some baseline attributes in the small groups with uncertain deficiency status. Controlling for these variables or omitting the groups with uncertain vitamin D status at the time of COVID-19 testing from the analysis did not change our findings.

Figure 1 depicts the distribution of most recent vitamin D levels between 1 year before and 14 days before COVID-19 test orders for the sample used in multivariable analysis (Table 2). Among the 35% of patients whose most recent vitamin D-level was deficient, 18% tested positive for COVID-19, compared to 12% for patients whose last vitamin D level was not deficient(p=0.11).

Follow-up and Outcomes

Table 2 shows the results of the multivariable GLM model for testing positive for COVID-19. Patients who were likely vitamin D deficient at the time of COVID-19 testing (i.e., their most recent vitamin D level before COVID-19 testing was deficient and they did not have their vitamin D dose increased) had an increased relative risk of testing positive for COVID-19(RR=1.77,p<0.02) compared to patients whose vitamin D level at the time of COVID-19 testing was likely sufficient (i.e., their last vitamin D level was not deficient and they at least maintained their vitamin D dose between the time of their last vitamin D level and when they were tested for COVID-19), for an estimated average rate in the vitamin D deficient group of 21.6%(95%CI[14.0%-29.2%]) versus 12.2%(95%CI[8.9%-15.4%]) in the vitamin D sufficient group. Testing positive for COVID-19 was also associated with increasing age, and non-white race, and was not associated with comorbidities except for a decreased incidence in persons with conditions associated with immunosuppression. Testing positive for COVID-19 was not significantly more likely for the patients classified as having vitamin D levels of uncertain sufficiency compared to patients with sufficient vitamin D levels. The risk of testing positive for COVID-19 in the likely deficient vitamin D group with a deficient last vitamin D level and no increase in treatment after that level was also not statistically significantly different than the risk of testing positive in the group with a deficient last vitamin D level but some increase in treatment. All these results were robust to including measures of time from last vitamin D level to COVID-19 testing. They also were preserved when the analysis was performed separately for non-white and white persons, though the small number of white persons forced dropping some covariates for model estimation in that subgroup. Because hypertension, obesity and diabetes may be ameliorated by treatment with Vitamin D, sensitivity analyses were also performed omitting these as covariates; this did not significantly change these findings.

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Among the 124 patients who had a deficient last vitamin D level and did not have vitamin D treatment increased, 60% had no recorded vitamin D treatment after the deficient level, 30% continued their dosing before the deficient vitamin D level, and the remaining 10% primarily reflected switches from vitamin D3 to vitamin D2 or from vitamin D2 to ≤1000IU vitamin D3. Among patients with a deficient last vitamin D level who had an increase in treatment after that level, 35% initiated or increased vitamin D3 to 2000IU or more, 50% initiated D2, and 15% initiated low-dose ≤1000 IU vitamin D3.

Vitamin D treatment type and dosage were not significantly associated with testing positive for COVID-19 (Table 3) but the analysis was notable for a small number of individuals receiving higher doses of vitamin D3. Vitamin D type and dosage were significantly ($p<0.01$) associated with deficient vitamin D levels (Table 4). The latter effect was no longer significant ($p=0.24$) if patients in the D3 2000IU and ≥3000IU categories were omitted from the analysis.

Discussion

This study provides the first direct evidence of the association of vitamin D deficiency and potentially insufficient treatment with testing positive for COVID-19. The multivariable analysis suggests that persons with deficient most recent vitamin D levels whose treatments were not increased and therefore likely remained vitamin D deficient were at substantially higher risk of testing positive for COVID-19 than were persons with levels that were likely to be sufficient.

This result supports the idea that having an insufficient vitamin D level increases the risk for COVID-19 and suggests that treatment for vitamin D deficiency can reduce that risk. The potential value of treatment for vitamin D deficiency in reducing the risk of COVID-19 is supported by the finding that patients with deficient last vitamin D levels who did have increased treatment were not found to have increased risk for COVID-19 compared to patients whose last vitamin D levels and treatments after those levels suggested they were likely to have had sufficient levels of vitamin D at the time they were tested for COVID-19. Though the difference in COVID-19 risk among these patients with deficient last vitamin D levels who were and were not treated did not reach statistical significance, the small fraction of those receiving treatment who received high dose vitamin D3 suggests that the ability identify an association of treatment in this sample is limited by relatively conservative treatment approaches used. That vitamin D treatment type and dose are related to rates of deficiency and that this association is fully accounted for by the two most effective treatments for vitamin D deficiency studied (vitamin D3 2000IU or ≥3000IU) reinforces the potential value of treatment.

Nevertheless, the complex relationship of treatments to COVID-19 risk and vitamin D levels and deficiency highlights the need for randomized trials to determine whether vitamin D treatment

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might affect the risk of COVID-19. Testing of vitamin D levels may be an important tool in guiding treatments, and the availability of low-cost home testing for vitamin D may be especially valuable given the benefits of social distancing in COVID-19. However, because vitamin D dosing of up to at least 4000IU or 5000IU is generally considered safe,[23] taking 4000-5000IU of vitamin D daily may be a reasonable approach for persons without known contraindications to vitamin D supplementation.

Although this appears to be the first data directly connecting vitamin D deficiency and the risk of COVID-19, the idea that adequate vitamin D levels could prevent COVID-19 is supported by multiple trials and meta-analysis that find vitamin D treatment can reduce other viral respiratory infections, among which coronaviruses are common causative organisms. While these benefits would be expected to be greatest among vitamin D deficient persons, the low risks of vitamin D supplementation, the costs and limited access to testing and known seasonality of vitamin D levels all argue for population-level supplementation efforts and perhaps targeted testing for groups at high risk for vitamin D deficiency and/or COVID-19, as noted above. Vitamin D deficiency is influenced by genetic factors, including in African Americans,[24] so Vitamin D testing and treatment may play an important role in reducing incidence among the African American community where COVID-19 has been particularly prevalent and morbid. This also implies that some risk for COVID-19 might be heritable, which might inform COVID-related decision making for persons with biological relatives who have been affected.

If the incidence of COVID-19 can be reduced by treatment with vitamin D, it is tempting to consider whether vitamin D might reduce COVID-19 transmission. However, caution is required because of the potential importance of asymptomatic persons in COVID-19 spread. Vitamin D is understood to modulate immune function through effects on dendritic cells and T cells[25], which may promote viral clearance and/or reduce inflammatory responses that produce symptoms. Higher vitamin D levels correlate with lower IL-6 levels, which is notable because IL-6 blocking agents are a major target for controlling cytokine storm in COVID-19.[26,27] Vitamin D may also affect metabolism of zinc[28], which has been found to decrease the replication of coronaviruses.[29] To the extent it decreases viral replication or accelerates viral clearance, vitamin D treatment might reduce spread. On the other hand, if vitamin D reduces inflammation, it might increase asymptomatic carriage and decrease symptomatic presentations, including cough, making it hard to predict its effect on viral spread.

Important limitations must be noted. First, the associations observed may not reflect causal effects of vitamin D deficiency on COVID-19, especially since vitamin D deficiency can reflect a range of chronic health conditions or behavioral factors that plausibly reduce the likelihood of treatment of vitamin D deficiency and increase COVID-19 risk. Nevertheless, the results are

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robust to including a broad set of demographic and comorbidity indicators. Our analysis also included patients treated with vitamin D2 or calcitriol, and included calcitriol levels in our definition of vitamin D deficiency, which are often used in patients with chronic kidney disease or hypoparathyroidism. In sensitivity analysis, our results generally strengthened when we omitted these patients. We also note our sample is enriched in persons with vitamin D deficiency because of the large number of African Americans, adults with chronic illness and health care workers, all living in a northern city and exposed to COVID-19 during winter. Vitamin D deficiency may be a smaller risk factor in other populations. The relative simplicity of the analysis performed here would facilitate replication of this analysis in other settings. Since vitamin D deficiency is so prevalent in the US population, and especially in persons with darker skin, who are older and nursing home residents, who are at increased risk for COVID, it seems likely that these findings might be replicated in other settings.

The data presented here argues strongly for a role of vitamin D deficiency in COVID-19 risk and for expanded population-level vitamin D treatment and testing and assessment of the effects of those interventions. Studies of whether interventions to reduce vitamin D deficiency could reduce COVID-19 incidence should be an important priority, including both broad population interventions and intervention among groups at increased risk of vitamin D deficiency and/or COVID-19.

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Table 1: Characteristics of Patient Population

			Full sample			Vitamin D Deficient (Most recent vitamin D in past year <20 ng/ml)		Not Vitamin D Deficient (Most recent vitamin D in past year ≥20 ng/ml)		Fisher's exact test for difference
			N	%		N	%	N	%	p-value
Number of patients			4314	100		178	100	321	100	
Age										
years (mean)			45.7			45.6		50.7		0.003 (t-test)
<50			2591	60		114	64	155	48	0.003
50-64			1040	24		34	19	89	28	
65+			683	16		30	17	77	24	
Gender										0.333
Female			2790	65		138	78	235	73	
Male			1524	35		40	22	86	27	
Race										<0.001
White			1067	25		30	17	128	40	<0.001
Other than White			2767	64		143	80	191	60	
Unknown			480	11		5	3	2	<1	
Ethnicity										1.000
Hispanic			249	6		15	8	28	9	
Not Hispanic			4004	93		163	92	293	91	
Unknown			61	1		0	0	0	0	
Employee status										0.553
UChicago employee			1431	33		63	35	104	32	
Not UChicago employee			2883	67		115	65	217	68	
Vitamin D level evaluated in past year			499	12		178	100	321	100	
Most recent vitamin D<20 ng/ml			241	6		178	100	0	0	
Vitamin D <20 ng/ml in past 2 years			305	7		178	100	54	17	<0.001
Recorded ICD-10-CM diagnosis of vitamin D deficiency in 2 years			251	6		71	40	100	31	0.061
Most recent vitamin D level within 1 year deficient (<20 ng/ml)?	Vitamin D dose stable, increased or decreased after last level?*	Interpretation								
Yes	Stable or decreased	Likely Deficient	127	25		127	71			
Yes	Increased	Uncertain deficiency	51	10		51	29			
No	Decreased	Uncertain deficiency	30	6				30	9	
No	Stable or Increased	Likely Sufficient	291	58				291	91	
Days since most recent vitamin D level (mean)			286			157		165		0.420
Days since most recent vitamin D level (median)			233			130		159		0.171
Comorbidity indicators										
Hypertension			1381	32		89	50	172	54	0.512
Diabetes			625	14		51	29	86	27	0.675
Chronic pulmonary disease			832	19		44	25	74	23	0.661
Pulmonary circulation disorders			82	2		9	5	11	3	0.475
Depression			451	10		46	26	75	23	0.585

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Chronic kidney disease	416	10		36	20	80	25	0.269
Liver disease	222	5		17	10	39	12	0.459
Comorbidities with immunosuppression	438	10		36	20	69	22	0.819
BMI value not missing	3656	85		177	99.4	320	99.7	1.000
BMI (mean)	29.8			30.5		29.4		0.158 (t-test)
BMI ≥30 kg/m^2	1593	37		90	51	141	44	0.159
Most recent active vitamin D treatment before COVID-19 test								<0.001
None	3502	81		83	47	135	42	0.347
1-1000 IU D3/Multivitamin	436	10		29	16	86	27	0.008
2000 IU D3	171	4		7	4	53	17	<0.001
3000+ IU D3	37	<1		10	6	10	3	0.232
D2	152	4		46	26	32	10	<0.001
Calcitriol	16	<1		3	2	5	2	1.000
Treatment adjustment after the most recent vitamin D level in past year	187	5		127	71	30	9	<0.001
Test positive COVID-19	758	18		32	18	40	12	0.110

* Vitamin D dose was rank-ordered as follows: Calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/Multivitamin > No Vitamin D.

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Table 2. Multivariable Association of Vitamin D Deficiency and Treatment with Testing Positive for COVID-19

			N	%	Relative Risk	p-value
Number of patients			489	100		
Age (Linear Spline)[§]						
<50			260	53	1.05	0.020
50+			229	47	1.02	0.063
Gender (Male is reference)			123	25		
Female			366	75	0.87	0.578
Race (White is reference)			158	32		
Race other than white			331	68	2.54	0.009
Ethnicity (Not Hispanic is reference)			448	92		
Hispanic			41	8	0.29	0.209
UChicago employee status (Not employee is reference)			328	67		
UChicago Employee			161	33	0.93	0.789
Most recent vitamin D level within 1 year deficient (<20 ng/ml)?	Vitamin D dose stable, increased or decreased after last level?*	Interpretation				
Yes	Stable or decreased*	Likely deficient	124	27	1.77	0.015
Yes	Increased	Uncertain deficiency	48	10	1.10	0.823
No	Decreased	Uncertain deficiency	30	5	1.09	0.851
No	Stable or Increased	Likely sufficient	287	59	reference	
Comorbidity indicators						
Hypertension			261	53	1.08	0.789
Diabetes			137	28	0.78	0.314
Chronic pulmonary disease			117	24	0.91	0.727
Pulmonary circulation disorders			20	4	0.64	0.398
Depression			119	24	1.22	0.442
Chronic kidney disease			116	24	0.80	0.388
Liver disease			56	11	0.99	0.983
Comorbidities with immunosuppression			105	21	0.39	0.005
BMI (mean)			29.8		1.02	0.098
Goodness-of-link test of squared predicted value[30]						0.866
Hosmer-Lemeshow goodness-of-fit decile test[31]						0.889

§ A piecewise linear spline with a single knot at 50 improved model fit over models with unadjusted age or more complex parameterizations.

* Vitamin D dose was rank-ordered as follows: Calcitriol > 3000+ IU D3 > 2000 IU D3 > D2 > 1-1000 IU D3/Multivitamin > No Vitamin D.

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Table 3. Bivariate analysis of most recent active vitamin D treatment 14 days before COVID-19 test order and COVID-19 test results, among patients with a diagnosis of vitamin D deficiency within 2 years or any level <20 ng/ml.

Most recent active vitamin D treatment prior to COVID-19 test order	Total patients	COVID-19 positive	
	N	N	%
No Vitamin D	180	23	13
1-1000 IU D3/Multivitamin	88	18	20
2000 IU D3	41	6	15
3000+ IU D3	25	2	8
D2	87	12	14
Calcitriol	7	2	29
Total	428	63	15
Fisher's exact test p = 0.399			

Table 4. Bivariate analysis of most recent active vitamin D treatment before most recent vitamin D level at least 14 days before COVID-19 test order and whether that level was <20 ng/ml, among patients with a diagnosis of vitamin D deficiency within 2 years or a level <20 ng/ml.

Most recent active vitamin D treatment before most recent vitamin D level	Total patients	Vitamin D Deficient (Most recent vitamin D in past year <20 ng/ml)	
	N	N	%
No Vitamin D	139	87	63
1-1000 IU D3/Multivitamin	92	50	54
2000 IU D3	38	13	34
3000+ IU D3	25	15	21
D2	107	73	68
Calcitriol	5	3	60
Total	406	241	59
Fisher's exact test p = 0.009			

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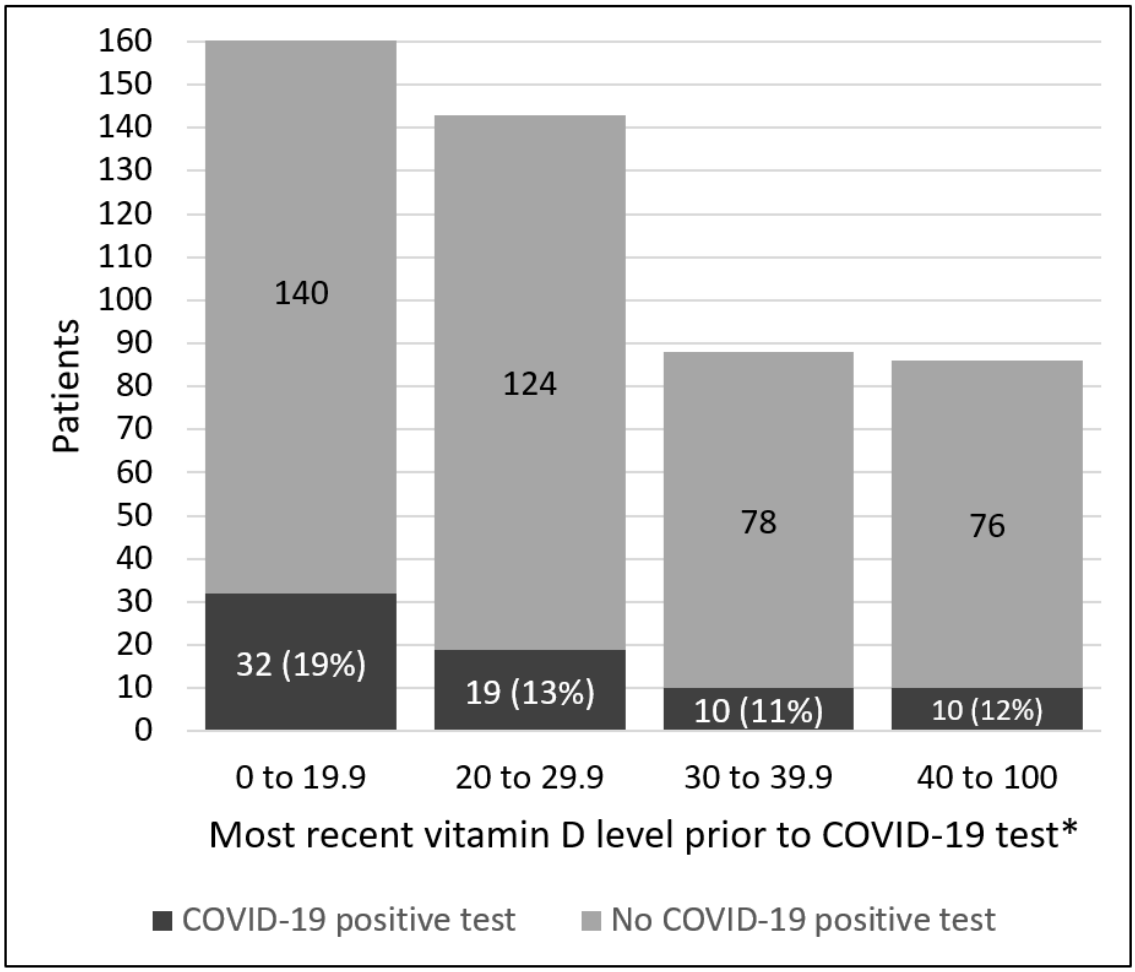

*Shown are the last vitamin D levels between 1 year before and 14 days before COVID-19 test orders (N=489 distinct patients). Seven levels are in pg/ml from a test of $1,25(OH)_2$-vitamin D and the remainder are in ng/ml from a test of 25(OH)-vitamin D.

Figure 1. Most recent vitamin D levels prior to COVID-19 tests

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Methodologic Supplement.

Chronic condition indicators. Each chronic condition indicator was set equal to 1 if the patient had at least one of a list of ICD-10-CM diagnosis codes included on an administrative/billing record with a discharge date between January 1, 2018 and April 10, 2020. The lists of codes used for the indicators was defined using the HCUP Elixhauser Comorbidity Software.[20] For each condition, we used all ICD-10-CM and DRG codes listed within categories in the Elixhauser file comformat_icd10_cm_2020_1.sas, entitled Creation of Format Library for Comorbidity Groups, ICD-10-CM Elixhauser Comorbidity Software, Version 2020.1. The actual ICD-10-CM codes can be found by finding the following category variable names in the file. Hypertension: HTN, HHRWCHF, HHRWHRF, HHRWOHRF, HHRWRF, HRENWORF, HRENWRF, HTNCX, HTNPREG, HTNWCHF, HTNWOCHF, OHTNPREG, HTNCXDRG, HTNDRG. Diabetes: DM, DMCX, DIABDRG. Chronic pulmonary disease: CHRNLUNG, PULMDRG. Pulmonary circulation disorders: PULMCIRC. Depression: DEPRESS. CKD: RENLFAIL, HHRWCHF, HHRWHRF, HHRWOHRF, HHRWRF, HRENWRF, RENALDRG, RENFDRG. Liver disease: LIVER. CM_IS: AIDS, METS, TUMOR, ARTH.

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Supplemental Table 1: Characteristics of Patient Population

	Full sample			Likely deficient		Uncertain deficiency: increased treatment		Uncertain deficiency: decreased treatment		Likely sufficient		Fisher's exact test for difference
	N	%		N	%	N	%	N	%	N	%	p-value
Number of patients	4314	100		127	100	51	100	30	100	291	100	
Age												
years (mean)	45.7			45.9		44.6		50.2		50.7		0.028 (ANOVA)
<50	2591	60		79	62	35	69	10	33	145	50	
50-64	1040	24		26	20	8	16	14	47	75	26	0.007
65+	683	16		22	17	8	16	6	20	71	24	
Gender												0.301
Female	2790	65		96	76	42	82	19	63	216	74	
Male	1524	35		31	24	9	18	11	37	75	26	
Race												<0.001
White	1067	25		22	17	8	16	8	27	120	41	<0.001
Other than White	2767	64		103	81	40	78	22	73	169	58	
Unknown	480	11		2	2	3	6	0	0	2	1	
Ethnicity												0.416
Hispanic	249	6		8	6	7	14	3	10	25	9	
Not Hispanic	4004	93		119	94	44	86	27	90	266	91	
Unknown	61	1		0	0	0	0	0	0	0	0	
Employee status												0.006
UChicago employee	1431	33		43	34	20	39	2	7	102	35	
Not UChicago employee	2883	67		84	66	31	61	28	93	189	65	
Vitamin D level evaluated in past year	499	12		127	100	51	100	30	100	291	100	
Most recent vitamin D<20 ng/ml	241	6		127	100	51	100	0	0	0	0	
Vitamin D <20 ng/ml in past 2 years	305	7		127	100	51	100	13	43	41	14	<0.001
Recorded ICD-10-CM diagnosis of vitamin D deficiency in 2 years	251	6		50	39	21	41	12	40	88	30	0.155
Days since most recent vitamin D level (mean)	286			149		178		134		168		0.092
Days since most recent vitamin D level (median)	233			119		168		112		161		0.049
Comorbidity indicators												
Hypertension	1381	32		65	51	24	47	21	70	151	52	0.227
Diabetes	625	14		30	24	21	41	11	37	75	26	0.066
Chronic pulmonary disease	832	19		35	28	9	18	8	27	66	23	0.475
Pulmonary circulation disorders	82	2		6	5	3	6	1	3	10	3	0.695
Depression	451	10		37	29	9	18	11	37	64	22	0.102
Chronic kidney disease	416	10		27	21	9	18	12	40	68	23	0.143
Liver disease	222	5		13	10	4	8	8	27	31	11	0.081
Comorbidities with immunosuppression	438	10		28	22	8	16	7	23	62	21	0.779
BMI value not missing	3656	85		126	99.2	51	100	30	100	290	99.7	0.660
BMI (mean)	29.8			30.2		31.2		28.8		29.5		0.451 (ANOVA)
BMI ≥30 kg/m^2	1593	37		60	47	30	59	12	40	129	44	0.247
Most recent active vitamin D treatment before COVID-19 test												<0.001
None	3502	81		72	57	11	22	8	27	127	44	<0.001
1-1000 IU D3/Multivitamin	436	10		19	15	10	20	15	50	71	24	0.001
2000 IU D3	171	4		3	2	4	8	1	3	52	18	<0.001
3000+ IU D3	37	<1		3	2	7	14	2	7	8	3	0.005
D2	152	4		27	21	19	37	4	13	28	10	<0.001

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Calcitriol	16	<1		3	2	0	0	0	0	5	2	0.853
Treatment adjustment after the most recent vitamin D level in past year	187	5		127	100	0	0	30	100	0	0	
Test positive COVID-19	758	18		26	20	6	12	4	13	36	12	0.183

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