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The effect of vitamin D Treatment on COVID 19-patients, an inverted propensity score weighting (IPSW), and inverted probability of treatment weighting (IPTW) analyzed study

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Abstract

Background: Vitamin D3 (1,25(OH)$_2$cholecalciferol) as a treatment for COVID 19 patients is being disputed, and a clear clinical benefit is not being confirmed.

Methods: A retrospective evaluation for COVID-19 patients who were treated with various cumulative doses of vitamin D. Data was extracted from the COVID-19 database, it included patients admitted to three hospitals in Amman, Jordan. Characteristics of patients were tabulated and compared for all-cohort, and propensity score index (PSI) adjustment. The comparison was based on two vitamin D strata (≤ 149,000 i.u. and > 150,000 i.u.). Logistic regression analysis was utilized to predict recovery, the need for oxygen, and all-cause mortality for all-cohort, IPSW, and IPTW patients, based on vitamin D cumulative doses during their hospital stay.

Results: 1131 all-cohort and 768 PSI-adjusted patients were recruited. Except for antibiotics and antivirals, all other characteristics were balanced (P = NS). There were 1017 patients on vitamin D, 847 received cumulative ≤ 149,000 i.u., and 170 patients received cumulative dose

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≥ 150,000 i.u. (Range 1000 – 385000). It was demonstrated that the escalation of the cumulative doses of vitamin D did not contribute to the assessed outcomes; all-cohort patients (OR = 1.000, 95% C.I. 1.000 to 1.000), IPSW (OR = 1.000, 95% C.I. 1.000 to 1.000), and the IPTW (OR = 1.000, 95% C.I. 1.000 to 1.000).

Conclusion: In our patients' cohorts, we could not demonstrate a beneficial effect for vitamin D therapy in COVID-19 patients in recovery, the need for home oxygen, and all-cause mortality, by hospital discharge.

Keywords
Vitamin D; COVID-19; COVID-19 Recovery; Covid-19 Mortality; COVID-19 the need for home oxygen therapy.

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Introduction

COVID-19 hit the world populations causing morbidities and mortalities, cure and/or mitigation are being sought. Several interventions are adopted in the treatment of COVID-19 without strong evidence, like an effective antiviral therapy [1-3], zinc and ascorbic acid [4], and convalescent plasma [5, 6]. Vitamin D3 (1,25(OH)$_2$ cholecalciferol) is being used in COVID-19 patients for its known immunomodulating effects, and its role in signaling during adaptive and innate immune responses in viral, and bacterial infections [7]. Previous studies associated the initial high serum levels, and vitamin D supplementations with reduced incidence of seasonal influenza or improvement in the duration and severity [8-10]

A large population-based observational study included 39,190 COVID-19 patients with low serum vitamin D levels (<20 ng/ml) had had higher positivity for SARS-CoV-2 (12.5%) compared with 27,870 patients with higher levels where they had lower positivity (8.1%), even 12,321 patients with values ≥55 ng/mL had positivity rates of 5.9%, in a multivariate analysis, the association rates between positivity rates and higher circulation Vitamin D was demonstrated (AOR 0.984 per ng/ml increment, P < 0.001) [11]. However, the use of vitamin D in COVID-19 patients have been linked to uncertainty, evidence supporting its use appeared as it was derived from a small RCT study detecting a reduction in COVID-19 severity in ICU patients, similar evidence came from other observational studies [12-14]

In the current study, we aim to illustrate the treatment effects of using vitamin D in COVID-19 patients. Our patients were prescribed different and varying doses during their hospital stay, to avoid confusion about regimens the total cumulative doses for vitamin D were evaluated to predict causal treatment effects.

Materials and Methods

Study Settings

Data for COVID-19 patients was collected from three participating hospitals (The Specialty, Jordan, and Al Khalidi) with a total bed capacity of around 700, special units for the management of patients with COVID-19 were allocated with an approximate capacity of 155-floor beds and 47 ICU beds. The study was a retrospective cross-sectional over 22 weeks (28 November 2020 to 6 May 2021), data was uploaded into a cloud excel sheet (*Microsoft Corporation*). Records were included as patients presented for admissions in the participating hospi-

tals. The study was approved by each of the internal review boards of the three hospitals, no consent was needed.

Treatment protocols

There is a current updated COVID-19 management protocol published by the Jordan Ministry of Health (MOH). In the three hospitals, the treating physicians partially relied on the MOH protocol and literature updates, the treatment protocol for vitamin D was heterogeneous (supplementary material); different doses, and may vary over the treatment period in the same patient. Vitamin D tablets (used as a three-day 50,000 I.U. regimen before March 15, then a seven-day 50,000 I.U., also a 2000 I.U. and 5000 I.U., daily were prescribed. Other agents administered; steroids (dexamethasone or solumedrol), anticoagulants (Enoxaparin sodium, Apixaban, Rivaroxaban, and Fondaparinux), antivirals (Favipiravir, Remdesivir), acetylsalicylic acid (ASA), colchicine, Zn tablets, and Vitamin C (supplementary material).

Classification of radiological findings

Chest radiography scoring system: the degree of lungs involvement was based on radiologists' classification for the degree of lungs involvement. Normal chest x-ray and/or normal CT chest with no infiltrate were considered as no involvement (score 1), a lobar infiltrate with 25% involvement (score 2), scattered ground glass appearance involving lungs with >25 - 50% involvement (score 3), diffuse patchy infiltrate >50 - 75% involvement was considered as (score 4), and multilobe infiltrate was considered as >75% involvement (score 5) [15].

Statistical analysis

Characteristics for the all-cohort and PS-adjusted patients were described, propensity-score match tolerance (caliper) was 0.1, without replacement, normal distribution for predictors was tested by skewness, histogram, P-P blot, and Q-Q blot, all fitted a normal curves distribution, skewness for all were < 1.0 and > -1.0, multicollinearity was evaluated by linear regression (tolerance was above 0.251, mostly > 0.8 and VIF was mostly less than 1.3 except two with 3.554 and 3.992), continuous predictors were evaluated by Levine's test and were homoscedastic. Predicted probability was derived from continuous and binary predictors thru binary logistic regression analysis, some continuous predictors were Log10-transformed to normalize the distribution before they were incorporated in the model (supplementary material). Predictors entered were: Age, gender, the sum of recorded symptoms, comorbidities, Log_BMI, Tobacco, Log_ferritin level, Log_D-Dimer, Log_LDH, imaging scores, steroids, antivirals, antibacterials, Antifungal, IL6-inhibitors, documented temperature, blood oxygen saturation, oxygen delivery method, and peripheral white blood cells [16, 17]. Vitamin D treatment was analyzed by Chi-square test (χ^2) astwo categories (<149,000,> 150,000) with post hoc analysis by Bonferroni adjusted p-value to assure balanced variables. IPSW patients were estimated for the outcome effects by Logistic regression analysis, it was tabulated for the all-cohort, PSM, and SIPTW patients. SPSS version 25 with Python Essentials and Fuzzy extension command blog-ins was used in the analysis, significance was considered for values < 0.05.

Results

The characteristics of the 1220 patients were reviewed, eighty-nine cases had missing data and were excluded. Analysis was for 1131 as the all-cohort, and 768 PSM and 768 PS-adjusted patients **(Table 1)**. The differences in characteristics between two vitamin D dose categories among the all-cohort were balanced with the PSI **(Table 1)**, few characteristics had significant (P < 0.05) but borderline imbalance with PS-adjustment. Age was balanced in the initial cohort except for the age group (Lowest thru 65 years), more patient proportions were in the higher vitamin D cumulative dose group (≤ 149,000 i.u.

Table 1. The characteristics of COVID-19 patients according to Vitamin D treatment allocations.

Characteristic		All cohort, Vitamin D			Propensity score-adjustedpatients		
		N = 1017			N = 768		
		≤ 149,000i.u.	≥ 150,000i.u.	P *	≤ 149,000i.u.	≥ 150,000i.u.	P *
		n = 847	n = 170		n = 639	n = 129	
Age (years)	Lowest thru 65	481 (56.9)	112 (65.9)	0.072	372	82	0.429
	66 thru 75	194	34		139	27	
	76 thru highest	171	24		128	20	
Gender	Male	544	405	0.542	413	82	0.817
	female	303	65		226	47	
Antivirals		537 (67.3)	73 (43.7)	<0.05	443 (69.3)	58 (45)	<0 .05
Antibiotics		656 (77.4)	81 (47.6)	<0.05	504 (78.9)	62 (48.1)	< 0.05
Antifungal		68	20	0.197	57	18	0.195
Colchicine		205	31	0.217	166	25	0.114
Presenting symptoms (Sum)		847	170	NS	639	129	NS
Documented fever		833	168	0.606	669	131	0.651
Comorbidities	Two or more	439	80	0.857	349	63	0.851
	Diabetes mellitus	49	12		35	11	
	Chronic lung disease	11	1		11	1	
	Heart disease	10	2		9	2	
	Hypertension	70	12		51	9	
	Malignancy	7	0		4	0	
BMI	Lowest thru 25	176	26	0.142	146	21	0.123
	26 – 30	295	71		240	60	
	31 thru highest	230	48		190	43	
	Tobacco use	99	12		80	10	
Blood oxygen saturation (%)	>94	174	34	0.179	117	21	0.380
	90 – 94	286	70		216	54	
	85 -89	184	35		149	29	
	80 -84	102	19		85	16	
	<80	88	9		72	9	
Oxygen delivery method	RA	121	15	0.318	88	9	0.516
	Simple mask	108	26		72	21	
	High flow	25	11		20	8	
	Noninvasive ventilation	34	4		29	3	
	Combined	36	7		30	7	
	IMV%	31	2		24	2	
	Non-rebreather mask	168	30		142	25	
	Nasal Prongs	309	72		245 (36.6)	56 (42.7)	

Characteristic		All cohort, Vitamin D			Propensity score-adjustedpatients		
		N = 1017			N = 768		
		≤ 149,000i.u.	≥ 150,000i.u.	P *	≤ 149,000i.u.	≥ 150,000i.u.	P *
		n = 847	n = 170		n = 639	n = 129	
Imaging score (X-ray and CT)	Normal	41	7	0.253	24	3	0.166
	25% Involvement	60	10		49	9	
	>25 – 50% Involvement	302	69		243	57	
	>50 – 75% Involvement	231	55		165	40	
	>75% Involvement	206	28		156 (24.4)	19 (14.7)	
Procalcitonin level (ng/mL)	≤0.5	286 (33.8)	91(53.5)	<0.05 NS	245	75	0.866
	> 0.5	101	26		82	24	
D-Dimer (ng/mL)	≤ 0.5	287	66	0.249	212	51	0.323
	>0.5 – 2	293	63		241	48	
	>2	209	33		181	30	
Ferritin ng/ml	<260	133	20	0.451	10.3 (16.1)	12 (9.3)	0.131
	260 – 1000	374	74		294	62	
	>1000	297	67		242	55	

Percent in (brackets) are proportions ofsub-variables when statistical significance was demonstrated.*: 2-sided Significance (P-value) was tested by χ2, and Bonferroni method.% Invasive mechanical ventilation. NS: not significant.

= 56.9% versus ≥ 150,000 i.u. = 65.9%, p < 0.05), however, all other categories were balanced in the PS adjustment. Gender remained well-balanced in the initial cohort (P = 0.542) and the PS-adjusted patients (P = 0.817). Antivirals and antibiotics were imbalanced in both all-cohort and the PS-adjusted patients (P < 0.05). Documented fever, comorbidities, BMI, tobacco use, and blood oxygen saturation were well balanced for both cohorts (P = NS). Oxygen delivery method was balanced for the all-cohort patients and PS-adjustment (P = NS) except for the nasal prongs, it remained imbalanced (P < 0.05) where more patients were in the vitamin D category > 150,000 i.u. Admission radiological imaging showed well balance in the all-cohort and PS-adjusted patients except it were imbalanced for the > 75% involvement. PCT levels were well balanced in both cohorts (P = NS), but imbalance was in the subcategory (≤ 0.5 ng/ml). D-Dimer levels were well balanced in both cohorts (P = NS). Serum ferritin was imbalanced for the subcategory (<260 ng/ml) in the PS-adjusted patient, both cohorts were well balanced (P = NS).

There were 1017 patients on vitamin D, 847 received cumulative ≤ 149,000 i.u., and 170 patients received cumulative dose ≥ 150,000 i.u.(Dose range 1000 – 385000), and the majority (823) was in ≤ 50,000 cumulative i.u.

Outcomes analyses

In the all-cohort analysis, recovery was in 401 patients, vitamin D supplement increasing cumulative dose did not significantly contribute to recovery (B = 0.000, S.E = 0.000, Wald = 4.076, P = 0.043, OR = 1.000, 95% C.I. 1.000 to 1.000), also, no significance was noted for IPSM (B = 0.000, S.E = 0.000, Wald = 187.905, P = 0.000, OR = 1.000, 95% C.I. 1.000 to 1.000), and IPTW (B = 0.000, S.E = 0.000, Wald = 278.483, P = 0.000, OR = 1.000, 95% C.I. 1.000 to 1.000). There were 455 patients

Table 2. The outcome of using Vitamin D in the treatment of the COVID-19 patients analyzed as all-cohort, propensity score adjustment, and inverted probability of treatment weight (IPTW) by logistic regression analysis.

Characteristic		B	S.E.	Wald	P	OR (ExpB)	95% C.I.
Recovery*	All-cohort	0.000	0.000	4.076	0.043	1.000	1 to 1
	IPSW	0.000	0.000	187.905	0.000	1.000	1 to 1
	IPTW	0.000	0.000	278.483	0.000	1.000	1 to 1
On home oxygen	All-cohort	0.000	0.000	16.421	0.000	1.000	1 to 1
	IPSW	0.000	0.000	164.703	0.000	1.000	1 to 1
	IPTW	0.000	0.000	207.543	0.000	1.000	1 to 1
All-cause Mortality	All-cohort	0.000	0.000	4.874	0.028	1.000	1 to 1
	IPSW	0.000	0.000	8.386	0.004	1.000	1 to 1
	IPTW	0.000	0.000	20.509	0.000	1.000	1 to 1

Percent in (brackets) are proportions ofsub-variables when statistical significance was demonstrated.*2-sided Significance (P-value) was tested by $\chi 2$, and Bonferroni method.% Invasive mechanical ventilation. NS: not significant.

discharged home on oxygen, no observable effect of vitamin D to avoid patients form using home oxygen (B = 0.000, S.E = 0.000, Wald = 16.421, P = 0.000, OR = 1.000, 95% C.I. 1.000 to 1.000), similarly no significance was for IPSM analysis (B = 0.000, S.E = 0.000, Wald = 164.703, P = 0.000, OR = 1.000, 95% C.I. 1.000 to 1.000), and IPTW (B = 0.000, S.E = 0.000, Wald = 207.543, P = 0.000, OR = 1.000, 95% C.I. 1.000 to 1.000).

Overall, all-cause mortality was 13.79% (156 patients), and for those who stayed in the ICU the mortality was 55.0% (110 patients). There was no significant effect for the cumulative doses of vitamin D on all-cause mortality (B = 0.000, S.E = 0.000, Wald = 4.847, P = 0.028, OR = 1.000, 95% C.I. 1.000 to 1.000), similarly no significance was noted for IPSM analysis (B = 0.000, S.E = 0.000, Wald = 8.386, P = 0.004, OR = 1.000, 95% C.I. 1.000 to 1.000), and IPTW (B = 0.000, S.E = 0.000, Wald = 20.509, P = 0.000, OR = 1.000, 95% C.I. 1.000 to 1.000) **(Table 2)**.

Discussion

With the advent of the COVID-19 pandemic and its high morbidity and mortality including more clotting, several organs inflammation, hypoxemia, and acute and chronic interstitial lung diseases that may end in fibrosis in some patients [18-20].Several interventions to alleviate the disease severity are being sought to handle the high morbidity and mortality associated with COVID-19, including several therapeutic interventions, steroids, anticoagulants, antivirals, and vitamin D (25-$(OH)_2$ cholecalciferol). Previous studies demonstrated that vitamin D had a favorable preventive effect in seasonal influenza A infection [21]. However, its therapeutic effects are being disputed until now [22, 23].

In our study, we evaluated the prescribed cumulative doses of vitamin D, and whether they have effects on alleviating COVID-19 patients, our primary interest was to evaluate the impact of the increasing cumulative doses of vitamin D on the outcomes; recovery by hospital discharge, the need for home oxygen therapy, and all-cause mortality.

Recovery from COVID-19 by hospital discharge as defined here: patients who did not need for home O2 therapy, and did not have the following symptoms offever, headaches, myalgias, loss of taste, loss of smell, and chills and other symptoms that were non-existent before COVID-19. In all-cohort, IPSW, and IPTW, vitamin D did not improve recovery in

COVID-19 patients (OR = 1, 95%C.I. 1 to 1). Also, it did not improve the rates of the need for home oxygen therapy for discharged patients (OR = 1, 95%C.I. 1 to 1). The all-cause mortality in our patients was 13.79% and the ICU mortality was 55%. However, patients analyzed as all-cohorts, IPSW and IPTW did not show any improvement with the increasing vitamin D cumulative dose (OR = 1, 95% C.I. 1 to 1).

Conclusion

In our patients' cohort, we could not demonstrate a beneficial effect for vitamin D as a therapy in COVID-19 patients for the measured outcomes; recovery by hospital discharge, the need for home oxygen therapy, and all-cause mortality. Those results confirm previous literature that demonstrated no clear clinical effects for using vitamin D as a therapy.

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