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Correlation of Vitamin D With D Dimer, Ferritin, LDH & CRP Levels in Patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) Infection - A Cross Sectional Study

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Abstract

SARS-COV-2 has been a global cause of illness and mortality in the recent years. Various literature published online postulated the hypothesis that Vitamin D level in the infected person plays a significant role in the disease severity. There is compelling evidence for an epidemiological association

between low serum 25-OH-D levels and human infections such as influenza. Some retrospective studies demonstrated a correlation between vitamin D status and COVID-19 severity and mortality, while other studies did not find the correlation when confounding variables are adjusted. Studies have shown that inflammatory markers like CRP, LDH, ferritin, D-Dimer can be used to predict severity of disease. The higher levels of markers predicted higher severity of disease.

Hundred and thirty RT-PCR positive patients were included in our study and correlation between vitamin D and other parameters like D Dimer, CRP, LDH, ferritin was done. Vitamin D correlated inversely with Ferritin, D-dimer and LDH and directly with CRP but correlation was statistically significant only with D-dimer and LDH. Ferritin was positively and significantly correlated with CRP & LDH, negatively correlated with D-dimer. D-dimer and CRP correlated positively and with significance. Low vitamin D levels correlated well with some biomarkers like LDH and D-dimer. At the same time no significant correlation was identified with ferritin and CRP.

Keywords

COVID 19, Vitamin D, D-dimer, LDH, CRP, ferritin.

Introduction

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) has caused a global pandemic of Coronavirus disease 2019 (COVID-19). The symptoms of the infected person range from mild to severe illness to death. According to the reports published 40-45% patients remain asymptomatic 30-40% develop mild symptoms and less than 15% cases develop severe disease (1). Literature published online postulated the hypothesis that Vitamin D level in the infected person plays a significant role in the disease severity.

Vitamin D is a seco-steroid with varied immunomodulatory, anti-inflammatory, antifibrotic and antioxidant actions. Several studies demonstrated the role of vitamin D in reducing the risk of acute viral respiratory tract infections and pneumonia by direct inhibition of viral replication and anti-inflammatory /immunomodulatory mechanisms. Vitamin D is a hormone with a pleiotropic role and there is compelling evidence for an epidemiological association between low serum 25OHD levels and human infections such as influenza, HIV, and hepatitis C virus infection (2,3). There is growing evidence that it may be responsible in the pathophysiological processes of COVID-19(4). The relationship between vitamin D deficiency and adverse prognosis has been suggested by the apparent Northern–Southern latitude gradient, with mortality and hospitalization rates for COVID-19 seen to be higher in northern latitude countries compared with those closer to the equator (5). A retrospective study, provides evidence of an association between vitamin D deficiency and adverse outcome in patients with COVID-19(6). Vitamin D inhibits cytokine storm syndrome be its immunomodulatory mechanism (7).

Extra-renal expression of CYP27B1 has been found in alveolar macrophages, dendritic cells, lymphocytes, and epithelia, which form 1,25(OH)2D3 locally to act in an autocrine or paracrine fashion to modulate cell proliferation, cell differentiation and inflammation (8). At the beginning stages of acute inflammation (elicitation phase), vitamin D inhibits proliferation of Th1 and Th17 cells and the abnormal release of their cytokines (IFN-γ, TNF□α, IL-1, IL-2, IL12, IL-23 and IL-17, IL-21) (7). During the resolution phase of inflammation, vitamin D-mediated

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differentiation of Th2 cells and release of their cytokines (IL-4 and IL 10) are important to avoid organ damage through an excessive immune response.

Mechanistically, vitamin D treatment can decrease mRNA expression of IFN-β and interferon-stimulated genes in respiratory syncytial virus (RSV). Down regulation of pro inflammatory cytokines is another important mechanism by which vitamin D exerts its immunomodulatory effects in the pulmonary infection. It has been reported to reduce downstream targets of TNF-α, directly modulate NF-κB activity in immune cells and indirectly inhibit NF-κB signaling by up regulating the expression of insulin-like growth factor binding protein-3 (IGFBP-3) (8). Additionally, vitamin D can decrease expression of IL-6 through MAPKs/P38 signaling pathway (9). Considering its role as a strong immune suppressor, vitamin D supplementation might help inhibit abnormal immune response and cytokine storm in COVID-19.

Studies have shown that inflammatory markers like C- reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D- dimer can be used to predict severity of disease. The higher levels of markers predicted greater severity of disease (10, 11). This study was done to correlate vitamin D levels with severity of SAR-COV-2 infection by trying to correlate above biomarkers/inflammatory markers D-dimer, LDH, CRP, ferritin.

Materials and Methods

Study design

Cross sectional cohort study Ethics approval: The study was approved by the institutional ethics committee and informed consent was taken from the all participants.

Study location

Department of Biochemistry in collaboration with Department of General Medicine, Mamata Academy of Medical Sciences Hospital, Bachupally, Hyderabad, a tertiary care centre

Study Duration

3 months from 1st August 2020 till 31st October 2020

Sample Size

130 RT-PCR Positive COVID-19 cases were included.

Inclusion criteria

Real time PCR tested positive Covid-19 patients of age between 21-90 years who survived and were discharged after treatment.

Exclusion criteria

Patients with liver disease, renal failure, nephrotic syndrome, patients on drugs like glucocorticoids, pregnant women, smokers and deceased patients were excluded from the study.

Methodology

Peripheral venous samples collected aseptically at admission, serum separated from it by centrifugation and investigations done immediately on daily basis. 25(OH) Vitamin D and Ferritin was estimated by CLIA method on Mindray CL1000i analyzer (Mindray, Shenzhen China). D-dimer was estimated by nephelometry on Mispa i2 immunoturbidimetry method kit. LDH was estimated by Kinetic method by Mindray BS240Pro analyzer. C-reactive protein was measured in latex enhanced immune-turbidimetric method by Merilyzer semiauto analyzer.

Statistical Analysis

was done by GraphPad Prism version 9.1.1 statistical software, in addition, all variables underwent a Pearson correlation analysis to gauge linear covariance between the outcome measures and the corresponding serum vitamin D concentration within

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cases cohort. For binary outcomes, a receiver operating characteristic (ROC) curve was plotted to assess the prognostic value of serum concentrations of vitamin D. Area under the curve (AUC) values >0.5 were deemed to convey a prognostic value in the measured variable.

Results

A total of 130 patients with mean age 52.25 ± 15.68 years, range 21–90; male (n=92): female (n=38), were recruited to the study (Table 1).

Mean value of Vitamin D levels was 24.87 ± 16.60 nmol/L with a minimum value of 4.35 and maximum of 90.54 nmol/L. The mean value of ferritin was 376.8 ± 428.5 ng/ml with a minimum of 1.8 ng/ml and maximum of 2023 ng/ml. D-dimer mean value was 491.5 ± 863.2 with a minimum of 100.0 microg/ml and maximum of 5000 µg/ml. The mean value of LDH was 288.4 ± 103.1 with a minimum of 105.0 IU/L and maximum 620 IU/L. The mean CRP level was 21.72 ± 28.37 mg/ml with a minimum of 6 mg/ml and maximum of 100.0 mg/ml (Table 2).

Vitamin D correlated negatively with Ferritin, D-dimer and LDH and positively with CRP but correlation was statistically significant only with D-dimer and LDH with a 'p' value of < 0.05. There was no statistically significant correlation with Ferritin and CRP (Table 3).

Ferritin was positively and significantly correlated with CRP & LDH, negatively correlated with D-dimer. D-dimer correlated positively to CRP which was statistically significant.

Assay range 0.1-150mg/ml, initial absorbance exactly after 5 second and final absorbance after exactly 240 sec after initial absorbance and CRP concertation was calculated. Reference range Low risk of CVD; 3mg/ml.

Table 1: Age and Gender Distribution of the Study Population

S. No	Age (years) All Cases	Male	Female	No of patients
1	20-40	28	7	35
2	41-50	19	1	20
3	51-60	26	13	39
4	61-70	13	10	23
5	> 70	6	7	13
Mean Age	**52.25 ± 15.68**	**49.43 ± 14.15**	**59.08 ± 17.24**	
	Total	**92**	**38**	**130**

Table 2: Descriptive statistics of all parameters among cases

	Ferritin	D Dimer	Vit D	CRP	LDH
Minimum	1.8	100	4.35	6	105
Maximum	2023	5000	90.54	106	620.6
Range	2022	4900	86.19	100	515.6
Mean	376.8	491.5	24.87	21.72	288.4
Std. Deviation	428.5	863.2	16.6	28.37	103.1
Std. Error of Mean	37.58	75.71	1.456	2.488	9.046

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Table 3: Pearsons Correlation r between Vitamin D and other markers among all cases

Vitamin D			
Parameters	**Correlation coefficient (r)**	**P value (two tailed)**	**Significance**
Ferritin	-0.08371	0.3437	Ns
D Dimer	-0.1847	0.0354	*
LDH	-0.2034	0.0203	*
CRP	0.008233	0.9259	Ns

P < 0.05* = Significant ns = not significant

Table 4: Pearson's Correlation in cases between all the Covid 19 markers

		Ferritin	D Dimer	Vit D	CRP	LDH
Ferritin	r value	1	-0.05371	-0.08371	0.194648	0.501443
	P value		0.544	0.344	0.026*	1.225e-009*
D Dimer	r value	-0.05371	1	-0.18466	0.228767	0.055856
	P value	0.544		0.035*	0.009*	0.528
Vit D	r value	-0.08371	-0.18466	1	0.008233	-0.20336
	P value	0.344	0.035*		0.926	0.020*
CRP	r value	0.194648	0.228767	0.008233	1	0.107389
	P value	0.026*	0.009*	0.926		0.224
LDH	r value	0.501443	0.055856	-0.20336	0.107389	1
	P value	1.225e-009*	0.528	0.020*	0.224	

Discussion

The main findings of our study suggest that patient's serum concentrations of 25(OH)D correlated significantly with serum LDH and plasma D dimer levels but it did not correlate significantly with Ferritin and CRP. In a study conducted by Baktash V et al it was found that vitamin D-deficiency was associated with higher peak LDH and ferritin levels which is in concordance with our study although significant correlation was not seen between Vitamin D and Ferritin. Mitra Kazemijahromi et al reported a significant correlation of Vitamin D and LDH among covid 19 patients in concordance with our findings (12).

In our study Vitamin D and D dimer are inversely related in concordance with a study by Jose et al where in COVID 19 patients, 25OH vitamin-D was inversely associated with some inflammatory parameters, such as ferritin and D-dimer, though we did not find any significance in its relation (13). In contrast to many other studies, vitamin D though inversely related to Ferritin there was no statistical significance.

In a study conducted by Kaftan et al it was found that serum ferritin, CRP, LDH were elevated significantly in covid 19 patients which is in concordance with our findings where in there is a

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positive and statistically significant correlation of ferritin with CRP and LDH (14).

In a study done by Almigdad H. M. Ali et al it was found that patients with COVID-19 have significantly higher serum levels of CRP, D- dimer and LDH which is in concordance with our study (15).

Conclusion

Vitamin D plays a major role in immunosuppression and immunomodulation. Low vitamin D levels correlated well with some biomarkers like LDH and D-dimer. At the same time no significant correlation was identified with ferritin and CRP. Our study is limited by small population study. In the randomized trials and meta-analysis, vitamin D supplementation has been shown to have protective effects against respiratory tract infections; therefore, people who are at higher risk of vitamin D deficiency during this global pandemic should consider taking vitamin D supplements. Some retrospective studies demonstrated a correlation between vitamin D and COVID-19 cases and outcomes, while other studies did not find the correlation when confounding variables are adjusted. Yet, there is insufficient evidence on the association between vitamin D levels and COVID-19 severity and mortality. Therefore, randomized controlled trials and large-scale cohort studies are necessary to test this hypothesis.

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