THE ASSOCIATION OF VITAMIN D CONCENTRATION WITH INTERLEUKIN-6 (IL-6), D-DIMER AND SEVERITY OF COVID-19 DISEASE IN A SAMPLE OF IRAQI POPULATION

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ABSTRACT

Background: Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a recently emerged, highly transmissible, and pathogenic coronavirus that has created global public health and economic crisis. Since December 2019, when Covid-19 emerged in Hunan seafood market in Wuhan, South China, and rapidly spread throughout the world, the virus outbreak has been declared a public health emergency of international concern by the World Health Organization (WHO). This research included several parameters (Vit-D, IL-6, and D-Dimer) to evaluate the association between these biomarkers and outcomes in COVID-19 hospitalized and non-hospitalized patients, to guide potential COVID-19 Diagnosis, Treatments, and Prevention of COVID-19 disease.

Aim of the study:

1- To determine if there is an association between the status of vitamin D level in blood and the severity of COVID19 disease.

2- To determine the association between vit-D level and (IL-6, and D-Dimer) levels in serum and their effect on these markers in the hospitalized COVID19 disease.

3- to evaluate the association between (IL-6, and D-Dimer) and the severity of COVID19 disease.

Methods:

A Cross-sectional study consisted of 40 patients with age range (18-90 years) that collected from ICU (hospitalized patients) in (West Irbil Governmental Hospital and Lalaf Governmental Hospital) in Erbil city/ Iraq, at admission to the hospital, and 40 patients with age range (18-90 year)there were non-hospitalized patients from the same place in Erbil city/ Iraq, from December 2020 to April 2021.

Serum( Vit-D, and IL-6), and plasma D-Dimer concentrations were measured, firstly to comparing them with (age, gender, and the severity of SARS-CoV-2 virus infection) to demonstrate the association of them with the severity of COVID-19 disease, and secondly to compared them with vit-D and demonstrate the effect of this vitamin on these parameters.

Results:

In the present study, the data showed A significant decrease in Vit-D concentration in sera of patients with SARS-CoV-2 virus infection in both groups, which determines the strong correlation in (two-tailed) between vit-D concentration and the severity of SARS-CoV-2 virus infection P-value (0.00001), as while as, there is a statistical correlation between the severity of COVID-19 disease and D-Dimer in both groups P-value (6.2E-9).
while statistically non-significant relation between the severity of COVID-19 disease in both groups and age P-value (0.79), also non-significant relation between vit-D and age p-value (0.08), and Non-significant correlation between gender and the severity of COVID-19 disease in both groups P-value (0.82).

In both groups, there is a significant negative correlation between vitamin-D and D-dimer concentrations in H group correlation P-value (0.0001), in the non-H group P-value(0.025).

Statistical analysis showed a significantly strong correlation between high IL-6 level and the severity of SARS-CoV-2 virus infection in both study groups non-H and H, P-value (0.00001).in comparison with severe deficiency of Vit-D that determines the strong correlation in (two-tailed) between vit-D concentration and IL-6 Conc. of SARS-CoV-2 virus infection.

Conclusion:

1- The results of this study reveal that vitamin D deficiency presents an association with the severity of COVID-19, Anecdotal and observational data indicate that vitamin D deficiency may play a significant role in the progression of the COVID-19 disease state.

In conclusion, the results confirm the high prevalence of vitamin D deficiency in people with COVID-19, we observed a positive association between vitamin D deficiency and the severity of the disease.

2- The current study revealed a significantly strong correlation between IL-6 and D-dimer with Vit-D levels, in hospitalized patients and non-hospitalized patients suggesting that Vit-D blood levels have an important effect on IL-6 and D-dimer levels that’s maybe a biomarker of disease severity and progression in patients with COVID-19.

3- According to the severity of COVID-19 disease, the present study showed a significant correlation between (vitamin-D, IL-6, and D-dimer) with the severity of COVID-19 disease suggesting that these parameters may be biomarkers of disease severity and progression in patients with COVID-19.

I. INTRODUCTION

Coronaviruses

Coronaviruses are a large family of viruses that may cause disease in animals or humans. Coronaviruses are a broad group of viruses that can infect both animals and humans. (Coronavirus disease (COVID-19). et al., 2020).

Seven coronaviruses can infect people all over the world, but the four most common human coronaviruses are 229E, NL63, OC43, and HKU1. They usually cause respiratory infections ranging from the common cold to more serious diseases like Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), as well as the newly discovered coronavirus. (Coronavirus disease (COVID-19). et al., 2021).

This zoonotic disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), This infectious disease was previously known as Novel Coronavirus-Infected Pneumonia (NCIP) by the WHO, and the virus was dubbed 2019 novel coronavirus (2019-nCoV). (Singhal, T.,2020).

Coronaviruses are large, enclosed, positive-stranded RNA viruses that infect a wide range of mammalian and avian species. Coronaviruses have spike-like projections of glycoproteins on their surface that resemble a crown when viewed under an electron microscope; thus, they are called coronaviruses.

S proteins are type-I transmembrane proteins that are clover-shaped and have three segments: a large ectodomain, a single-pass transmembrane, and an intracellular tail. The S1 subunit, which contains a receptor-binding domain (RBD), and the membrane-fusion subunit make up the ectodomain of S proteins (S2). (Wu F, Zhao S, et al., 2020).

Coronavirus 2 (SARS-CoV-2) Coronaviridae viruses are enveloped single-stranded, positive-sense RNA viruses. The Betacoronavirus genus, contains all of the highly pathogenic CoVs, including SARS-CoV-2. The genomic sequence of SARS-CoV-2 shows 80% sequence identity with SARS-CoV and 50% with MERS-CoV. (Lu, R. et al. 2020).
Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a recently emerged, highly transmissible, and pathogenic coronavirus that has created global public health and economic crisis. (Qiu Y, Zhao Y-B, et al., 2020).

This virus is a member of the Coronaviridae family, which is part of the Nidovirales order. The coronavirus family is divided into four subgroups: alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus. The four ‘common human coronaviruses’ are 229E (α coronavirus), NL63 (α coronavirus), OC43 (β coronavirus) and HKU1 (β coronavirus).

SARS-CoV-2 is a β-coronavirus. β-coronaviruses also include SARS-CoV and MERS-CoV, other acute-lung-injury causing coronaviruses of zoonotic origin. SARS-CoV-2 is most closely related to SARS-CoV, sharing roughly 80% identity at a nucleotide level. (RKI - Coronavirus SARS-CoV-2, et al., 2020).

1.3.2. The structure of SARS-CoV-2

SARS-CoV-2 encapsulated viruses have large (26-32 kbs) single-stranded, positive-sense RNA genomes and have a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope. Spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins are among the 16 nonstructural proteins found in the genome, S1 and S2 are the two subunits of the S protein, S1 is involved in viral entrance into host cells and contains the receptor-binding domain (RBD). (CDC. Coronavirus Disease, et al., 2020).

**Cell entry and viral replication** The S protein of SARS-CoV-2 interacts with Angiotensin-converting enzyme 2 through the RBD, allowing the virus to connect to the cells (ACE2), SARS-CoV also has a functional receptor called ACE2, which is found on the surface of lung alveolar epithelial cells and small intestine enterocytes, ACE2 is found in arterial and venous endothelial cells, as well as arterial smooth muscle cells throughout the body.

Following receptor binding, the virus must gain access to the host cell cytosol, which usually involves proteolytic cleavage of the S protein followed by the fusing of the viral and cellular membranes in coronaviruses. (Malik YS, et al., 2020).

Recent SARS-CoV-2 data suggest that the protease TMPRSS2 is involved in priming the virus's S protein for membrane fusion. Fusion results in the release of the viral RNA genome into the cell cytoplasm.

According to CT-value analysis, the G614 variation is associated with potentially greater viral loads, but not with illness severity. Nonetheless, higher viral loads may not always imply more transmission potential, and the argument over whether G614 is more infectious than D614 continues, as Grubaugh et al. excellently highlighted. (Du, P.; et al., 2020).

However, like with influenza, it is yet unknown if, in the long run, a progressive accumulation of mutations could result in SARS-CoV-2 antigenic drift, which could affect vaccination effectiveness. (Gomez-Carballa, et al., 2020).

Clinical manifestations ranging from no symptoms to mild fever, cough, and dyspnea to cytokine storm, respiratory failure, and death were established as human-to-human transmission events. To identify individuals who would have rapid disease progression, significant complications, and death, new biomarkers are required. (Kermali M, et al., 2020).

Since then, more research and meta-analyses have been conducted, confirming a median incubation period of 5 to 6 days. Yang et al. found that 95 percent of symptomatic individuals developed symptoms within 13.7 days (95 percent CI 12.5–14.9) of infection, and 99 percent by 17.8 days (95 percent CI 15.9–19.7) of infection in a study of 178 cases and 131 transmission chains in Hubei province. (Woelfel R, et al., 2020).

Efficient host cell entry depends on:
(i) cleavage of the S1/S2 site by the surface transmembrane protease serine 2 (TMPRSS2); and/or
(ii) endolysosomal cathepsin L, which mediate virus–cell membrane fusion at the cell surface and endosomal compartments, respectively. (Snijder, E.J. et al., (2006))

The RNA genome is released into the cytosol via either entry method, where it is transcribed into replicase proteins (open reading frame 1a/b: ORF1a/b). A virus-encoded protease cleaves the polyproteins (pp1a and pp1b) into individual replicase complex nonstructural proteins (nsps) (including the RNA-dependent RNA polymerase: RdRp). (Perlman, S, et al., 2020).

Severe vitamin D deficiency is defined as a serum 25(OH) D level of less than 30 nmol/L, according to the European Calcified Tissue Society Working Group. Male chronic obstructive pulmonary disease patients had mean 25(OH) D concentrations of 16 (95 percent CI 13–18) ng/mL, while female patients had concentrations of 13 (95 percent CI 11–15) ng/mL, according to an Italian study. (Paul Lips KDC, et al., 2014).

Patients with community-acquired pneumonia (CAP) had a mean 25(OH)D concentration of 14±8 ng/mL at hospital admission, according to a research in South Korea. (Malinovschi A, et al., 2015).

A study in Iran reported that hypertensive patients had lower 25(OH)D concentration. (Naghshtabrizi B, et al., 2017) Ilie et al. (SACN vitamin, et al., 2020) found a crude association between the mean vitamin D levels in various European countries with COVID-19 cases and COVID-19 mortality. (Chirumbolo S, et al., 2020).

Overview of the role of vitamin-D: Vitamin D, a seco-steroid, can be made in the skin from a cholesterol-like precursor (7-dehydrocholesterol) by exposure to sunlight or can be provided pre-formed in the diet. The skin version is known as vitamin D3, whereas the dietary form can be vitamin D3 or a closely related molecule of plant origin known as vitamin D2. Because vitamin D may be produced in the skin, it is sometimes referred to as a prohormone, and the two forms are referred to as cholecalciferol (D3) and ergocalciferol (D4), respectively (D2). (Feldman, D.et al., 1997).

Severe vitamin D deficiency is also linked to an increase in inflammatory cytokines. The serum levels of 25(OH)D and TNF-alpha were found to have a strong inverse association in a study of healthy women in the United States. (Alhassan Mohammed H, et al., 2017).

The levels of IL-6 were shown to be higher in those who were vitamin D deficient in another study. Vitamin D3 has been shown to reduce the production of inflammatory cytokines including TNF-alpha and IL6, while raising inhibitory cytokines in a range of animal experiments and in vitro cell models. These findings suggest that high vitamin D levels may minimize the occurrence of cytokine storms, which can occur in COVID-19. (Giannis D, et al., 2020).

In COVID-19 individuals, thrombotic problems are prevalent. D-dimer levels were found to be high in almost half of patients with severe illness. Vitamin D is also involved in the control of thrombotic pathways, and vitamin D deficiency is linked to a higher risk of thrombotic events. (Mohammad S, et al., 2020).

Vitamin D can increase Treg levels T-regulatory lymphocytes (Tregs) are a key barrier against uncontrolled inflammation, The number of Tregs is significantly lower in patients with severe COVID-19 infection, whereas elevated Treg levels have been linked to a lower level of respiratory viral disease, suggesting that adequate vitamin D levels may reduce the cytokine storm that can occur in COVID-19 infection. Furthermore, thrombotic problems are common in COVID-19, and vitamin D deficiency has been linked to an increase in thrombotic events, raising further questions regarding the need for adequate vitamin D intake. (Panarese A, et al., 2020).
D-dimer elevations in COVID-19 patients may be useful in identifying those with severe disease, pulmonary problems, and a high risk of venous thromboembolism in the setting of a pro-thrombotic condition. This would help with risk categorization and the early implementation of COVID19-related morbidity and mortality reduction strategies. Patients with severe forms of COVID-19 have greater D-dimer concentrations than those with milder variants, according to a new meta-analysis. (Lippi G, et al., 2020).

Experimentally induced viral lung infection, where IL-6 may have contextual protective or exacerbating roles including the severity of infection, survival, and tissue remodeling, has provided clues as to how increased levels of IL-6 and other cytokines impact immunity, but there is very limited data on coronavirus family members in general. (Wang Z, et al., 2020)

Study design and groups:

A Cross-sectional study consisted of 40 patients with age range (18-90 years) that collected from ICU (hospitalized patients) in (West Irbil Governmental Hospital and Lalaf Governmental Hospital) in Erbil city/ Iraq, at admission to the hospital, and 40 patients with age range (18-90 year), there were non-hospitalized patients from the same place in Erbil city/ Iraq.

serum (Vit-D, and IL-6) and plasma D-Dimer concentrations were measured and comparing them with (age, gender, and the severity of SARS-CoV-2 virus infection) to demonstrate the association of vit-D with the severity of COVID19 disease.

Statistical analysis

Statistical analysis Data was collected and analyzed using SPSS (Statistical Package for the Social Science) version 25 program was used to detect the effect of different factors in study parameters. An independent t-test was used to significantly compare between means. Pearson correlation and Spearman correlation were used to estimating of the correlation coefficient.

Demographic and Clinical Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Tested value</th>
<th>non-H*</th>
<th>H*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D3(ng/ml)</td>
<td>25.61±13.22</td>
<td>15.35±14.80</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

The study was included 80 individuals infected with the SARS-CoV-2 virus were recognized by PCR test (+ve result), 40 samples of them were non-hospitalized subjects (23 Male and 17 female). They had signs and symptoms of COVID-19 disease but they didn't need to enter ICU, and 40 samples of them have hospitalized subjects (22 Male and 18 female). They had signs and symptoms of COVID-19 disease with severe infection and low Spo2 and they needed to enter ICU.

3.1. The concentration of blood Vitamin D3 versus severity.

In the present assay, vitamin-D concentration was determined in Cobas e 601 immunoassay analyzers for estimation of the concentration of Vit.D in sera of patients with SARS-CoV-2 virus infection, normal range (≥30 ng/ml). The mean of Vit.D concentration results are shown in the table (3.1.1).

The mean of vitD concentration in the non-H group was (25.61±13.22), while in the H group was (15.35±14.80), We can note that there is a severe deficiency of Vit.D in these two study groups.

Table (3.1.1): Comparison of concentration serum vitD between study groups.
A significant decrease was shown in Vit.D concentration in sera of patients with SARS-CoV-2 virus infection in both groups, which determines the strong correlation in (two-tailed) between vitD concentration and the severity of SARS-CoV-2 virus infection P-value (0.00001) as shown in table (3.1.2).

3.2. Age versus severity in study groups

80 patients (45 males and 35 females) with mean ±SD age in non-H group (48.1 ±18.4) years and in H group with mean ±SD (49.12±14.97) age range between 18-85 years who confirmed to have COVID-19 were enrolled in this study, shown in table (3.2.1).

Statistically non-significant relation between the age and the infection with SARS -CoV-2 virus in both groups P-value (0.79).

Table 3.2.1: Comparison of age distribution between study groups.

<table>
<thead>
<tr>
<th>Correlation test</th>
<th>COVID19 severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td></td>
</tr>
<tr>
<td>Spearman Correlation</td>
<td>0.028</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.80 NS</td>
</tr>
</tbody>
</table>

Non-significant correlation between age and the severity of SARS-CoV-2 virus infection in both study groups (non-H & H), P-value (0.08), shown in Table (3.2.2).

3.3. Gender versus severity.

Of the 80 patients who tested positive for SARS-CoV-2 virus, 45 subjects were male (56.25%) and 35 female (43.75%), in details 40 subject were non-hospitalized group (23 Male (57.5%) and 17 female(42.5%)), and 40 subject were hospitalized group (22 Male (55%) and 18 female(45%)), as shown in table (3.3.1).

Table 3.3.1: Comparison of gender distribution between study groups.
As shown in Table (3.3.2), non-significant correlation between gender and the severity of SARS-CoV-2 virus infection in both study groups (non-H & H), P-value (0.82) > (0.05).

Table 3.3.2: Correlation between the severity of SARS-CoV-2 virus infection and gender in study groups.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>57.5%</td>
<td>42.5%</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>56.25%</td>
<td>43.75%</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

3.4. Vitamin D3 concentrations versus D-Dimer concentrations.

In the present assay, D-dimer concentration was determined in Nano-Check (Rapid immune-chromatographic assay) analyzers for estimation of this parameter in sera of patients with SARS-CoV-2 virus infection.

As shown in Table (3.4.1), the mean of D-dimer concentration in the non-H group was (702.91±1126.48), normal range (<500 ng/ml) while in the H group was (2827.28±1681.73). It obviously can be seen there is an observed increment in D-dimer level in these two patients groups, especially in the H group.

Statistical analysis showed a significantly strong correlation between high D-Dimer level and the severity of SARS-CoV-2 virus infection in both study groups non-H and H, P-value (6.2E-9*).

Table 3.4.1: Comparison concentration of serum D-dimer between study groups.

<table>
<thead>
<tr>
<th>Tested value</th>
<th>non-H</th>
<th>H</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Dimer (ng/ml)</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>6.2E-9*</td>
</tr>
<tr>
<td></td>
<td>702.91±1126.48</td>
<td>2827.28±1681.73</td>
<td></td>
</tr>
</tbody>
</table>

As shown in Table (3.4.2), in the correlation between vitamin-D and D-Dimer in sera of patients with SARS-CoV-2 virus infection, In both groups there is a significant negative correlation between vitamin-D and D-dimer concentrations that’s mean when vitD level decrease D-dimer level increase; in H group there is strong correlation P-value (0.0001), and in the non-H group P-value(0.025) < 0.05.

Table 3.4.2: Correlation between vitamin-D and D-dimer in study groups.

<table>
<thead>
<tr>
<th>Correlation test</th>
<th>D-Dimer (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum vit.D3(ng/ml)</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td>non-H</td>
<td>0.367</td>
</tr>
<tr>
<td>H</td>
<td>- 0.56</td>
</tr>
</tbody>
</table>
### Table 3.7.1: Comparison concentration of serum IL-6 between study groups.

<table>
<thead>
<tr>
<th>Correlation test</th>
<th>IL6 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum vit.D3(ng/ml)</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>-0.38</td>
</tr>
</tbody>
</table>

*:*<0.05

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### Table 3.7.2: Correlation between IL-6 and Vit.D concentrations in study groups.

<table>
<thead>
<tr>
<th>Correlation test</th>
<th>IL6 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum vit.D3(ng/ml)</td>
<td>Pearson Correlation</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*:*<0.05

### II. DISCUSSION

#### 4.1. Concentration of serum Vitamin D3 in patients with COVID-19 disease and its association with the severity of this disease.

Regarding the results shown in (table 3.1.1) and (table 3.1.2), the present study agreed with (Raharusun P, et al., 2020) who showed that All of the investigations linked a lower 25(OH)D concentration to a more severe illness status (composite severity). Furthermore, Vit-D was linked to composite severity in trials that were corrected for confounders and those that were not. In all of the primary studies, there was a clear link between Vit-D and composite severity.

This finding also agreed with the study of (Alipio M, et al., 2020) who showed that A negative correlation has also been found between mean vitamin D concentrations and the number of COVID-19 cases in different countries. In adult COVID-19 patients, vitamin D deficiency has been linked to worse clinical results and mortality. Vitamin D concentrations and COVID-19 concentrations in children are being studied in terms of clinical severity and inflammation markers.

Wu, Z, et al., 2020 study showed the baseline prevalence of VDI (Vitamin D insufficiency) amongst ICU patients was 30-40%. In this study, we found that 84.6% of COVID-19 ICU patients had VDI, vs. 57.1% of floor patients. Strikingly, 100% of ICU patients less than 75 years old had VDI. We also found that 62.5% had CAC, and 92.3% had lymphopenia. Given these data, we hypothesize that VDI enhances COVID-19 severity via its prothrombotic effects and its derangement of the immune response.

Several other studies have also linked low concentrations of serum vitamin D to SARS-CoV-2 infection.

However, our study reports the associations between lung, clinical and laboratory parameters (including 25OHD concentrations) in elderly patients hospitalized for COVID-19, focusing on lung involvement. Accordingly, the mean age of analyzed patients was very high and this did not permit further comparison of vitamin D concentrations between COVID-19 patients and controls by stratifying different ages.

4.2. The association of age and gender with the severity of COVID-19 disease.

As showed in tables (3.2.1), (3.2.2), (3.3.1), and (3.3.2), the present study agreed with (Weir E.K. et al., 2020) study who didn’t found a correlation between age and COVID-19 patients (p = 0.77), Multiple linear regressions using age, gender, and the number of comorbidities (with vitamin D as the dependent variable) did not identify statistically significant effects of the independent variables on 25OHD level in COVID-19 patients.

The present results are not agreed with the (Munshi, R. et al., 2021) study which reported that patients over 60 years old had a long illness course and a higher proportion of instances with respiratory failure. Male patients had a significant difference (25.0 versus 21.0 days; p=0.036), whereas female patients did not.

The difference in the results may be due to the number of subjects that were included in this study, and the immunity of the population in this area. The hospitalized patients were males and females in variable age groups required ICU admission and mechanical ventilation, independent of age and gender.

4.3. Concentration of Vitamin D3 and its association with the concentration of D-Dimer in patients with COVID-19 disease.

As found in the table (3.4.1), the present results agree with (Zhou F, et al., 2020) who showed that D-dimer concentrations are commonly elevated in patients infected with SARS-CoV2. Significantly higher concentrations are found in those with critical illness and may be used as a prognostic marker for in-hospital mortality.

Also, these results agree with (Lippi G, et al., 2020) who showed that the serum concentrations of D-dimer, a fibrin degradation product that is used to diagnose the presence of a pro-thrombotic state, are significantly higher in patients with severe COVID-19 when compared to those with non-severe forms.

Several studies have shown that D-dimer concentrations are associated with the severity of community-acquired pneumonia and clinical outcome (Coronavirus disease (COVID-19), et al., 2020).

On the other hand the result in table Regarding present results in (table 3-1) shown significant correlation between vitamin-D and D-dimer concentrations in sera of patients with SARS-CoV-2 virus infection, in H group there is strong correlation P-value (0.0001), in the non-H group P-value(0.025) < 0.05.

Present results agreed with (Rastogi, A. et al., 2020) who showed that vitamin D serum concentrations negatively correlated also with D-dimer (r = −0.37, p = 0.04), C-reactive protein (r = −0.38, p = 0.04)

While these results note agreed with (Wu, C. et al., 2020) who showed Serum 25-OHD concentrations were not associated with concentrations of inflammatory and coagulation markers.

The difference of correlation between vitamin-D and D-dimer concentrations in these two groups can be explained depending on the severity of the disease.
4.6. The association of Interleukin-6 concentration with Vitamin D3 concentration and the severity of COVID-19 disease.

Results of the table (3.7.1) agreed with (Xu, X. et al., 2020) who showed that IL-6 was elevated in COVID-19 patients with severity of COVID-19 disease and it is also can be considered a relevant prognostic marker. It has been reported that mortality is higher in patients with elevated concentrations of IL-6. Therefore, IL-6 and IL-6R are receiving more attention as potential therapeutic targets for the treatment of COVID-19. Chen, Y. et al., 2020 disagreed with our results, they showed no correlation detected between Vit-D and IL-6 values in their cohort study. Moreover, in patients with very low Vit-D concentrations, the IL-6 values were slightly, but not significantly, more elevated in comparison with patients with higher Vit-D concentrations. This result may be attributed to the sample size used in the study.

Regarding results showed in a table (3.7.2), results were agreed with (Liu J, et al., 2020) who showed that the analysis identified a significant effect of Vitamin D administration on IL-6 (p < 0.05). IL-6 and COVID-19 outcomes, and, in particular a meta-analysis, these findings support a role for Vitamin D prescription, both prophylactic, and, potentially as a specific therapy.

Also agreed with (Chen N, et al., 2020) who showed VitD deficiency has been correlated with increasing concentrations of IL-6.

Although this study reported that VitD induced gene expression of IL-6, they showed the biochemistry of IL-6 changes in the presence of Vit.D to induce anti-inflammatory cytokine IL-10 instead of the pro-inflammatory cytokine, IL-17.

III. CONCLUSIONS

1. The results of this study reveal that vitamin D deficiency presents an association with the severity of COVID-19, Anecdotal and observational data indicate that vitamin D deficiency may play a significant role in the progression of the COVID-19 disease state.

2. In conclusion, the results confirm the high prevalence of vitamin D deficiency in people with COVID-19, we observed a positive association between vitamin D deficiency and the severity of the disease.

3. the current study revealed a significantly strong correlation between IL-6 and D-dimer with Vit-D levels, in hospitalized patients and non-hospitalized patients suggesting that Vit-D blood levels have an important effect on IL-6 and D-dimer levels that’s maybe a biomarker of disease severity and progression in patients with COVID-19.

4. According to the severity of COVID-19 disease, the present study showed a significant correlation between (D-dimer, IL-6, and Vit-D) with the severity of COVID-19 disease suggesting that these parameters may be used as biomarkers of disease severity and progression in patients with COVID-19.

Recommendations

1. From this perspective results, evaluating blood vitamin D levels must be considered in the clinical practice of health professionals and hospitals.

2. Due to the significant correlation of (D-dimer, IL-6, and Vit-D) with the severity of COVID-19 disease, these parameters must be considered in the clinical practice of health professionals and hospitals.

3. Due to the strong association between blood Vit-D levels and (the inflammatory biomarker "IL-6") and its association with (coagulation biomarker "D-dimer"), It must be taken into consideration the deficiency of Vit-D levels in the patients with COVID-19 disease and must be treated with vitamin D administration until reaching the optimal range of 40–60 ng/mL during all the year.

4. Moreover, vitamin D supplementation could be considered in patients with vitamin D deficiency and insufficiency, if they have COVID-19.

REFERENCES


