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FULL PAPER

Evaluating the level of vitamin D in Iraqi covid-19 patients and its association with biochemical parameters

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Vitamin D deficiency is widespread in Iraq country. Infectious rate with COVID-19 was increased in our country. Aim of this study to was to show more info on the relation between serum vitamin D level and infection's severity and its relation per other biomarker. This cross-sectional descriptive type that made in COVID-19 infected persons (n=90) attending abograib Hospital, from July 2021 to February 2022, 2020, who were confirmed for COVID-19 infection with RT-PCR. Divided according to the severity as not severe & severe. In this study, 90 patients infected with COVID-19 (age of the patients range from (18 - 65) years old were studied. There were 37 as not severe infected group (13female, 24 male), and 53 severe infected as 21 females, and 32 male. Level of Serum Vit. D significantly lesser in severe group than those in not severe group (14.2 ± 5.23vs. 31.11± 8.72 ng/ml) respectively. Serum D-dimer, Ferritin, and CRP parameters are significantly lower in in severe group than those in not-severe group (2.23 ± 1.51 vs 0.45 ± 0.32), (620.31 ± 189.56 vs 298.1±194.74), and (63.81 ± 35.2 vs 16.53 ± 12.82) respectively. Vitamin D level was negatively correlated with D-dimer, Ferritin, and CRP levels. This study showed that serum level of Vit. D was lesser in severe group, and it is negatively correlated with other inflammatory marker as D dimer, ferritin, CRP.

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KEYWORDS

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Introduction

Worldwide alleviation hard work is persistent to control the level of transmission of COVID-19. A wide-ranging area with common conditions being either mild symptoms or non-symptomatic and little illnesses as respiratory failure or acute respiratory distress syndrome and sometimes multi-organ defects are noticed in COVID-19 [1].

The detection for infection of human corona-virus has changed noticeably during this period. Qualitative PCR techniques of oral swabs, nasopharyngeal or broncho-alveolar lavage fluid are now considered as standard for finding it worldwide. Sometimes the nasopharyngeal swab could fail the diagnosis of SARS-COVID due to reducing the sample taken technique and it will lead to repeating the sample taking to find the diagnosis [2].

The infection of the virus will make tissue damage by the augmented release of several pro-inflammatory cytokines, and draught of pro-inflammatory granulocytes and macrophages. It will also lead to the activation of many cells like CD8, CD4 and T cells. This results in what is called cytokine storm (CS). It is also identified as macrophage activation syndromes or secondary hemophagocytic

lympho-histiocytosis, which can lead to tissue damage [3]. The responses of the body are antivirally presented by adaptive immunity and host innate. Those lead to inhibit the spread of inflammatory process and virus, and clean the diseased cells [4]. In this response, a synergistic input of both adaptive and innate immunity with the essential association between stages of pro-inflammatory cytokines, the disease severities, and subsets of immune cells have been established. Severe COVID-19 infection shows a CS inevitably continuing to ARDS and similarity to the secondary hemophagocytic lymphohistiocytosis (sHLH) [5].

Vitamin D is formed in the skin as 7-Dehydrocholesterol (7 -DHC), and is altered to pre-vitamin D, which isomerizes by non-enzymatic method to vitamin D. Then in the liver, it is hydroxylated, and then in the renal, it is further hydroxylated to form Calcitriol, which is the metabolically active form of Vitamin D [6].

Vitamin D and innate immunity involve the creation of both pro- inflammatory and anti-inflammatory cytokines. This is demonstrated by its relationship with many autoimmune infections [7]. Vitamin D can tolerate numerous of the toll-like receptors which are motivated by the gratitude of some pathogens. This leads to the release of cytokines and it may create antimicrobial peptides and reactive oxygen species. These peptides, such as cathelicidin, can affect the pathogens by neutralizing endotoxins and troubling their cell membranes and it reduces the viral load and its effects. The cathelicidins are known to have some anti-bacterial properties, and not only for bacteria but also for viruses and fungi [8].

Vitamin D affects ACE2/Angiotensin, augmenting the manifestation of ACE2, which is recognized to defend against respiratory tract infections that lead to acute lung injury and disorders related with cytokine hyper production, pneumonia, and ARDS [9].

Vitamin D efficacy has been recognized in seasonal influenza, seasonal infection in the northern areas where winters are severe, and populations who have low vitamin D levels. Among the infection of other viruses, the efficacy of vitamin D as an added therapy along with other anti-viral agents has also been mentioned in infection of Dengue [10].

Vascular damages are linked with COVID-19 infection where vitamin D rises the production of vascular endothelial growth factor which endorses the repair of vascular endothelial. Vitamin D insufficiency is categorized to augment the risk of endothelial dysfunctions, thrombosis, and pathological variants of the vascular system [11].

Consequently, there is a possible role of vitamin D in the infection with SARS-CoV-2 on the basis of its effects, adaptive and innate immunity, cardiovascular effects, the immune response and pro-thrombotic properties [12]. In the elderly period, the disease can affect the one with little vitamin D levels because when age increases the vitamin D levels will decrease, principally due to diminished contact to sunlight and also due to decrease in cutaneous synthesis which is one of its main provider in the body [13].

COVID-19 infection can cause severe thromboembolic problems in severe patients with the influence of the cytokine storm. D-dimer is the fibrin degradation product that is secreted in the circulation of the body when the blood clot thaws through fibrinolysis. The researchers recommended that the increase of D-dimer levels could guess disease severity, thromboembolic incident, and lung complication before they can happen. Thus, they aimed to decrease the disease' mortality and morbidity with early judgment [14].

Hypoxaemia makes vasoconstriction that leads to decreasing blood flow, endothelial damage, inflammation, vascular occlusion, and the main comorbidities such as age, diabetes, and long bed rest amongst other factors [15].

Regarding Ferritin is a key moderator of immune dys-regulation, especially under

excessive hyperferritinemia, through direct immune-suppressive and pro-inflammatory properties that affect the cytokine storm. Fatal results of COVID-19 have been recognized to be associated with cytokine storm syndrome, specifying that the severity of the disease depends on the cytokine storm syndrome. Ferritin ranks were high in patients who died from COVID-19 upon admission to the hospital and through the hospital stay. Raised levels of ferritin were also informed [16].

The general inflammatory effects to the serious acute respiratory syndrome of coronavirus-2 infection, which is a mark of COVID-19, almost all of the hospitalized patients had non-typical inflammatory biomarkers [17].

The C-reactive protein (CRP), which is an acute-phase protein defined by Tillet, and Francis, is manufactured in the liver as a response to interleukin-6 (IL-6), and it is a widely presented inflammatory biomarker [18]. An increase of CRP concentrations is linked with acute renal injury, and cardiovascular disease in surgical persons, with incident venous thromboembolism and with inflammatory rheumatic illnesses such as gout [19]. However, most documents about the relationship between early CRP concentration elevation, VTE and acute renal injury in COVID-19 patients were uncertain. The relation between D-dimer and CRP concentrations, the degradation of fibrin produces a link with thrombosis, have not been cleared [20]. Prior to global pandemic infection of COVID-19, up to about 90% of all clear raises in concentration of CRP indicate to an infectious aetiology, maximum frequency from a pathogen such as bacteria [21].

Material and methods

This study (cross-section) was conducted at Aboghraib Hospital, for the period from July 2021 to February 2022. 90 patients with COVID-19 infection recognized by PCR were studied. The age of the patients ranged from (18 - 65) years old.

The samples of blood were taken from the patients after acquiring their agreements. The data of the patients were obtained by conducting a questionnaire. The tests were done in the hospital.

Inclusion criteria: In this study, the age range of the patients infected with the corona virus was from (18-65) years old. They were with normal complete blood count.

Exclusion criteria: In this study, patients with past medical history of myocardial infarction, hematological disorder, hepatic disorder, and infection other than COVID-19 were excluded.

Whole blood samples were collected in clot activator tubes. The sample was later centrifuged clotting for 5 minutes at 3000 rpm. Clear serum was taken which was, then, divided into five eppendorf tubes (0.5 mL each eppendorf tube). Then, the serum was frozen at -50 °C.

The 25(OH)D level was revealed in patients by taking of 10–12 µL for investigation by an automated kit technique via the Electro-chemiluminescence enzyme immunoassay (Roche; cobas e 411).

By using the standard tube or with separating gel for this test, the serum was collected. 25-hydroxyvitamin D is unchanging at 20–25 °C for eight hours. Examples with precipitates were centrifuged before measurement in 2 hours. The smallest recognition limit is 3.0 ng/mL.

To measure D-dimer, the human whole blood was collected in tube with sodium citrate, and then the sample was centrifuged. Plasma D-dimer measurement had to be done within 24 hours.

Vidas ferritin is an automated quantitative test for measuring human ferritin in human serum or plasma by using Enzyme Linked Fluorescent Assay (ELFA).

NycoCard CRP is an analytical assessment for quantifiable purpose in human of C-reactive protein. "Abbott was the company label".

Patient groups

1. Group (1), which is symptomatic with infection by COVID-19, included (53) severe symptomatic patients with positive nasal swab (PCR).
2. Group (2), which included (47) patients, had positive nasal swab (PCR) result for COVID-19 infection, but as mild or asymptomatic.

The infection severity by COVID-19 was measured via a score called (modified National Early Warning). It consisted of the following: O_2 supplementation, age, heart rate, respiratory rate, systolic blood pressure, O_2 saturation, level of consciousness, and temperature [22].

Results

TABLE 1 Distribution of patients according to gender and the infection severity

	Not sever (N)	Sever (N)	
Female	13	21	P= NS
Male	24	32	

Patients according to Age

The most commonly observed kind of age was < 50 years (N = 37, 41.1%) in non-severe group, as compared with > 50 years (N= 53, 58.9%) in severe group.

TABLE 2 Level of parameters findings in patients with COVID-19 according to the infection severity

Parameters	Severe Mean ±SD	Not Severe Mean ±SD	P-Value
Vitamin D (ng/mL)	14.2 ± 5.23	31.11± 8.72	**P<0.01**
D-dimer (µg/mL)	2.23 ± 1.51	0.45 ± 0.32	**P<0.01**
Ferritin (ng/mL)	620.31 ± 189.56	298.1±194.74	**P<0.01**
CRP (mg/L)	63.81 ± 35.2	16.53 ± 12.82	**P<0.01**

Comparison of Vitamin D, D dimer, Ferritin, and CRP level between groups

The difference was significant in the level of vitamin D between the COVID-19 patients' groups, P< 0.01. The mean of severe group patients (14.2 ± 5.23 ng/mL) was significantly lower than the mean of non-severe group (31.11± 8.72 ng/mL).

The difference was significant in the level of D-dimer between the COVID-19 patients' groups, P < 0.01. The mean of severe group patients (2.23 ± 1.51 µg/mL) was significantly higher than the mean of the non-severe group (0.45 ± 0.32 µg/mL).

The difference was significant in the ferritin level between the COVID-19 patients' group, P< 0.01. The mean of severe group patients (14.2 ± 5.23 ng/mL) was significantly more than the mean of the non-severe group (31.11± 8.72 ng/mL).

The difference was significant in the CRP level between the groups of COVID-19 patients, P< 0.01. The mean of the severe group patients (63.81 ± 35.2 mg/L) was significantly higher than the mean of the non-severe group (16.53 ± 12.82 mg/L). These results are indicated in Table 2.

TABLE 3 The Correlation results between vitamin D and other found parameters in patients

Parameters	Vitamin D (ng/mL)	P-Value
D-dimer (µg/mL)	**r = - 0.51**	**P < 0.05**
Ferritin (ng/mL)	**r= - 0.35**	**P < 0.05**
CRP (mg/L)	**r = - 0.42**	**P < 0.05**

The relationship of vitamin D with inflammatory markers in patients infected with COVID-19 (severe and not severe patients)

The results present a correlation that was significantly negative, as observed between vitamin D level with D dimer level, P< 0.05, and the correlation coefficient was (r = - 0.51). The correlation between the level of vitamin D with the ferritin level was significantly negative as P< 0.05 and the correlation coefficient r = - 0.35. The correlation between the level of vitamin D with the CRP has significantly negative results as P < 0.05, and the correlation coefficient r value= - 0.42, as presented in Table 3.

Discussion

In the present study, we found a significant difference in the levels of vitamin D among the patient groups. These findings contribute to increasing the evidence-base that propose that the insufficiency of vitamin D can be linked with more serious consequences related to the infection of COVID-19 [23]. Definitely, the studies (pre-clinical) demonstrate that vitamin D encourages the immune response and epithelial cells of the respiratory system to discharge materials, such as cathelicidin, which is considered as an anti-microbial peptide that can free the respiratory pathogens. Vitamin D also starts the adaptive immunity to reduce many of the pro-inflammatory cytokines and it will lead to opposing COVID-19 outcomes [24].

Only a minority of other studies verified the relationship between the COVID-19-related deaths and the vitamin D deficiency [25].

Relations between the severe COVID-19 infection with vitamin D insufficiency have been recorded in epidemiological studies. A retrospective study revealed that insufficiency of vitamin D was not linked with the severity of COVID-19 [26]. In another study, about 82.2% of patients who were hospitalized due to COVID-19 infection had deficiency of vitamin D. Another study stated that deficiency of vitamin D (less than 10 mg/mL) in patients hospitalized for COVID-19 infection either moderate-to-severe, and who were prone to be longer stay in the hospital, was likened with higher serum level of vitamin D with no clear relationship with increased mortality rates [27].

As for D dimer, ferritin, and CRP levels; there was a significant difference between the patient groups in the present study.

The results agreed with Li Y. *et al*. [28] who found that the patients with serious infection with COVID-19 had a greater D-dimer than non-severe infection in the patients without cardiovascular disease.

Some authors [29] establish that the patients scheduled for anticoagulation weren't exposed to thrombotic complications, and this will highlight the possibility of early use of anticoagulation.

Other studies showed that the serum level of D-dimer can represent an appropriate finding of outcomes in patients infected with COVID-19, nevertheless, the greatest of these revisions have been restricted due to many causes such as the size of sample and/or use of varied questionable methods, and all of these used a static D-dimer measurement [30]. In a study of about 191 patients, a level of serum D-dimer more than 1 µg/ml was indicator of poor prognosis results [31].

In agreement with the previous studies, our results found a relation of higher D-dimer with disease development in infection of COVID-19, and this supported that the

hypothesis that severe infection had a great threat of hypercoagulability [32]. Moreover, many pieces of evidence hint about the non-surviving COVID-19 show a significant rise in serum D-dimer levels, and this will be reflective of increased coagulability grade. These findings recommend that increase in the level of D-dimer in COVID-19 infected patients could specify the thrombotic risk. Numerous techniques clarify the increased D-dimer level associated with hypercoagulability status in COVID-19 [33]. Some studies stated the anti-coagulation plans for patients with critical COVID-19 infection. Recent studies showed better outcomes with anticoagulation in COVID-19 patients [34].

The D-dimer level is higher in COVID-19 patients, the expressive of a greater risk for the development of the disease can also indicate a greater threat for thrombotic occasions. D-dimer is stated to be a significant predictive issue [35].

Some authors [36] establish that the patients scheduled for anticoagulation weren't exposed to thrombotic complications, and this will highlight the possibility of early use of anticoagulation.

Pastora J., et al. assessed many studies that matched the level of ferritin in patients admitted to the hospital among the survivors and non-survivors rate, and they confirmed that non-survivor patients displayed a level of ferritin on admission nearby 1400 ng/mL, which is about 3 and 4 times more than that detected in survivor patients [37].

In a previous study that studied about 298 patients infected with COVID-19, the patients who lost their lives had increases in the level of CRP about 10-fold greater than that of the survived patients (100.0 vs. 9.7 mg/L significant difference). Recent reports similarly recognized the relations between the level of CRP required ventilation of respiratory failure, with an approximately 5 times larger threat of an ARDS. They also reported that the high-sensitivity CRP of more than 5 mg/L matched with patients who had a lower CRP measurement [38]. The CRP was linked to extra-pulmonary disease in patients with COVID-19 infection, and it was associated with cardiac. Furthermore, a number of recent series reported a relationship between increased level of CRP with disease severity in patients with COVID-19 [39].

In our present study, we calculated the correlation between level of serum vitamin D and markers of inflammation that used to evaluate the severity of COVID-19 infection. Significant negative relationships were found between level of vitamin D and markers of inflammation such as a D-dimer, Ferritin and CRP level. In agreement with our results, Daneshkhah *et al.* [40] found that increased CRP was inversely associated with the level of vitamin D. Our outcomes suggest a possible part for vitamin D in reducing the complications due to the cytokine storm, and CRPcan be considered as an important sign and pointer for the severity of infection of COVID-19. Furthermore, Ricci *et al.* [41] established a significant association between enlarged D-dimer level with low vitamin D level. The association between the vitamin D level and inflammatory diseases has led to many arguments because the relation between the low level of vitamin D with enlarged inflammatory cytokines has not been completely discovered. A recent study conducted by Kazemi *et al.* [42] found that the relationship between the deficiency of vitamin D and inflammation of lung was contrary, and the bond between the low level of vitamin D and mortality rate was vague. Yousefzadeh *et al.* [43]. Another clarification was achieved by Camargo and Quraishi [44]. It stated that the low level of vitamin D might be due to the low vitamin D binding protein level, and this could be attributed to the interstitial leakage increased by greater vascular permeability through many inflammatory syndromes. Additionally, Waldron *et al*. [45] proposed that serum vitamin D was an adverse acute stage reactant, and an acute damage by inflammatory process.

TABLE 4 Comparison with other studies

Author	Year	Country	No. of patients	Conclusion
Eugene Merzon	2020	Israel	7807	The lower level of vitamin D is a self-determining risk for COVID-19 infection and hospitalization.
Harvey W. Kaufman	2020	US	191,779	Infection of COVID-19 positivity is strongly and inversely associated with the level of Vitamin D.
Dieter De Smet	2021	US	186	Small level of vitamin D is associated with stages and mortality of COVID-19 infection.
Ashu Rastogi	2022	India	89	Deficiency of vitamin D- per SARS-CoV-2 patients turned SARS-CoV-2 RNA negatively with a significant reduction in fibrinogen on high-dose cholecalciferol supplementation.
John P Bilezikian	2020	The US	RA	Activities of vitamin D on several organs will elevate the potential relations with mechanisms that CoV-2 virus contaminates human beings.
Karahan S.	2021	Turkey	149	Vitamin D was self-sufficiently linked with COVID-19 mortality. .
Puja Mehta	2020	The UK	NM	Documentation and management of hyper-inflammation by current, official treatments thru established well-being outlines to report the direct requirement to decrease the increasing death.
Angeliki M. Angelidi	2021	The US	144	Level of vitamin D is negatively related with invasive mechanical ventilation and mortality.
Marta Entrenas Castillo	2020	Spain	76	Vitamin D extensively decreased the management in ICU, and it diminishes the severity of COVID-19.
David O. Meltzer	2020	The US	489	Deficiency of vitamin D level is related with increased risk of COVID-19.
Anshul Jain	2020	India	372	Vitamin D supply to COVID-19 patients reduces the complications.
E. Laird 1.	2020	NE	UN	The level of vitamin D had a benefit for health in patients with COVID-19.

Conclusion

Deficiency of vitamin D is considered as a threat reason for insufficient innate, reactivity of immune system, and the infection severity.

Therefore, checking vitamin D would be required as a portion of the consistent wellbeing grade. The assessment was further required in chronic diseases persons, as we assume the deficiency of its level, and an amplified load of threat features for severity, additional illness, and increased incidence of death.

To sum up, this study settles that the decrease level of vitamin D level was linked with the infection severity and with increased markers of inflammation of COVID-19.

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Conflict of Interest

There are no conflicts of interests.

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