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Highlighting the Treatment Regimens used in COVID-19 Epidemic in Iraq with Special Regards to Vitamin D

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Abstract

Corona virus disease 2019 (COVID-19) is a flu-like infection caused by a novel virus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Severe cases of COVID 19 may lead to organ failure and even death. The aims of this study are highlighting the management protocols and the supportive therapy (especially vitamin D), and manifesting the severity of the clinical symptoms of patients in Iraq. A retrospective cross sectional study was conducted among 200 patients and their descriptive parameters for data were calculated to analyze the results. The mean age was 42.56±17.49 years and the majority of patients had mild to moderate symptoms (78%). There were many different pharmacological treatment regimens and different doses and durations of vitamin D. In conclusion, non-specific treatment protocols were used without compliance to the national guidelines for the treatment of COVID-19 patients in Iraq, and a wide range of pharmaceutical agents was administered without monitoring their safety and efficacy. Vitamin D was administered in different doses and durations without depending on the basal serum concentration.

Key words: COVID-19, Vitamin D, Treatment protocol, Iraq.

تسليط الضوء على نظم العلاج المستعملة خلال وباء كوفيد ١٩ مع اهتمام خاص بفيتامين د

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الخلاصة

يعد مرض فيروس كورونا ٢٠١٩ (كوفيد ١٩) عدوى شبيهة بالإنفلونزا ناتجة عن فيروس جديد يُعرف باسم فيروس كورونا ٢ المتلازمة التنفسية الحادة الوخيمة (SARS-CoV-2). تؤدي الحالات الشديدة من كوفيد ١٩ الى فشل الأعضاء او الموت. تتم معالجة مرضى كوفيد ١٩ باستعمال العلاجات الداعمة والأدوية التي يُتوقع أن تكون فعالة ولكن لايوجد علاج نهائي للمرض. تهدف هذه الدراسة إلى تسليط الضوء على بروتوكولات العلاجات فضلا عن العلاجات الداعمة وخاصة فيتامين د واستعراض شدة الأعراض السريرية لدى المرضى في العراق. أجريت دراسة مقطعية بأثر رجعي على ٢٠٠ مريض وتم حساب المعلمات الوصفية للبيانات وتحليل النتائج. كان متوسط العمر ٤٢,٥٦ ± ١٧,٤٩ سنة وغالبية المرضى عانوا من أعراض خفيفة إلى متوسطة (٧٨٪). هناك العديد من أنظمة العلاج الدوائي المختلفة وتم أخذ جرعات عشوائية على فترات مختلفة من فيتامين د من قبل المرضى. نستنتج من هذه الدراسة انه تم استخدام بروتوكول علاجي غير محدد للمرضى دون الامتثال للإرشادات الوطنية لعلاج مرضى كوفيد 19 في العراق مع إعطاء مجموعة واسعة من العلاجات الدوائية التي تتطلب المراقبة من أجل سلامتها وفعاليتها, ولقد تم إعطاء فيتامين د بجرعات وعلى فترات مختلفة دون الاعتماد على تركيزه الابتدائي في مصل الدم.

الكلمات المفتاحية: كوفيد ١٩، فيتاميد د، البروتوكول العلاجي، العراق.

Introduction

The coronavirus disease of 2019 (COVID-19), caused by SARS-CoV-2, has caused a major impact on the global health and economics since its emergence at the end of 2019. On 29 October 2021, more than 245 million cases and over 4.9 million deaths have occurred globally since the start of the pandemic. In Iraq 2,052,123 cases and 23,083 deaths have been reported till the date mentioned above[1].

For mild cases, supportive treatment is used by providing continuing hydration, nutrition, vitamins, and antipyretic; whereas oxygen therapy was used for hypoxic patients in advanced stages and it required multiple pharmacological therapies[2]. Most of the pharmacological medications used for COVID-19 were obtained from previous experience of drugs used during the (SARS-CoV) or Middle East Respiratory Syndrome coronavirus (MERS-CoV) pandemics due to their expected activity with no definitive success of treatment yet[2]. The United States Food and Drug Administration (FDA) advocated the therapeutic effect of many antiviral therapies[3,4]. Favipiravir, a polymerase inhibitor attracted attention for COVID-19 treatment due to its large spectrum of antiviral properties. As an oral drug, it is easy to be administered to asymptomatic or mild cases. Early administration was found to be effective in reducing viral load, as well as improving the clinical and radiological outcomes[5,6].

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Remdesivir, and Rebavirin proved their activity against COVID 19[7,8]. Lopinavir, in combination with Ritonavir, reported antiviral activity against SARS-CoV by reducing the viral load, improve the clinical symptoms and halt the progression of lung damage. They were used as an emergency treatment for COVID-19 patients in USA, Japan and other countries[9].

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are antimalarial drugs that have been proposed to be effective against COVID-19[10]. Later, results from systematic review and meta-analysis studies on the two drugs indicated their low efficacy in reducing mortality or lowering the risk of hospitalization in outpatients[11].

A study conducted by the WHO demonstrated that about 70% of COVID-19 patients received antibiotics, although 8% only had an evidence of superimposed bacterial infections[12]. At the beginning of the pandemic, unverified researches recommended the combined administration of Chloroquine / Hydroxychloroquine with the macrolide antibiotic Azithromycin[13]. Another factor that encourages the use of macrolide antibiotics is the potential immunomodulatory effects causing down regulation of pro-inflammatory cytokines by an unknown mechanism[14]. Nowadays, the clinical course of disease, laboratory tests, and imaging are required to assess if the COVID-19 patient has bacterial co-infection and requiring empirical antibiotic therapy[15].

Advanced disease may cause the release of high levels of pro-inflammatory cytokines (interleukins (ILs), tumor necrosis factor (TNF)-α, C-reactive protein (CRP), ferritin, and D-dimer. This is known as the cytokine storm, which requires the use of immunomodulatory drugs and can lead to sepsis, shock, respiratory failure, multi-organ dysfunction, and death[14]. Tocilizumab is a recombinant human monoclonal antibody and is considered as a therapeutic option for severely ill patients with extensive lung lesions and high IL-6 levels[16]. Interferons (IFNs) are cytokines with antivirals and immunomodulatory activity causing direct inhibition of viral replication and supporting an immune response to clear virus infection[17]. However, more clinical studies are needed to prove their significance.[18].

The plasma collected from healthy donors after recovery from a recent infection (convalescent plasma- CP) contains high neutralizing antibody titer (NAT), these expected to provide immediate passive short-term immunity and could prevent the infection without major safety concerns[19]. On 24th March 2020, the FDA approved the use of CP for patients with serious or immediately life-threatening COVID-19 infections[20].

Many studies were conducted to assess the benefit of anticoagulation in COVID-19 patients and show that using low molecular weight heparin (LMWH) resulted in higher lymphocyte and lower IL-6 levels compared to control patients, indicating an improvement in coagulation parameters and normalization of immunity[21].

Supplements (like vitamin A, C, D, copper, selenium, zinc) are of great importance in the prevention of symptoms after viral or bacterial infections[22]. A special concern was given to vitamin D due to its valuable impact on both innate and adaptive immunity, in addition to its role in the treatment of acute respiratory tract infections and other viral infections[23]. Yet, there is insufficient evidence on the association between vitamin D levels and COVID-19 severity and mortality [24]. It was observed that the COVID-19 patients with vitamin D deficiency had poorer outcomes with longer stay in the intensive care unit (ICU) and higher mortality rates[25]. Many reasons for vitamin D deficiency such as sun exposure time regarding to occupation, sun exposure surface area, old age and diet[26]. Old people also have comorbid diseases and take more than five medications and found to be prescribed a potentially inappropriate medication[27]. Although the exact level of vitamin D for its immunomodulatory action is unknown, however, it has been proposed that > 30 ng/ml is required to decrease the COVID-19 severity and mortality[28].

The aims of the study is highlighting the pharmacological treatments and supportive therapy (especially vitamin D) used by COVID-19 patients in Iraq, and manifesting the severity of the clinical symptoms presented during the course of the disease.

Patients and Methods

A retrospective, cross sectional, observational study was conducted among 200 patients who have recovered from COVID-19 recently. The data collection was conducted from February till April 2021.

Convenience sampling technique was used in the study. Patients from both genders at any age were included, they used vitamin D during the treatment of active disease and agreed to participate in the study. Exclusion criteria were patients who did not take vitamin D during the infection, did not respond to phone calls, pregnant women, and those whose information were incomplete.

The study protocol was approved by the Scientific Committee of the department and the college counsel, and it was conducted in accordance with the 1994 Declaration of Helsinki. Verbal consent was also taken from each patient, in addition to ethical approval (No. 2709 in 14th Jan. 2021) from the primary health care sector (Aladel sector Primary Health Care, Directory of Health Alkarikh, Ministry of Health). Data collected include patients' characteristics, pharmacological regimens used, and the dosing of vitamin D supplement. In addition to information about COVID 19 symptoms and

complications after the recovery were collected and used to classify disease severity as: patient with no symptoms, mild to moderate, severe and critical cases . Data related to the infection (symptoms, and treatments) were obtained from patient data, and was recorded by the treating physicians in the primary care center and from the patients through phone calls (duration of sun exposure in minutes per day, and the complications after the recovery). The researchers from primary health care centers in Baghdad / Alkarikh and Baaquba Teaching Hospital conveniently selected patient data sheets.

All the collected data was assembled and analyzed using an excel spreadsheet. Study findings were demonstrated by descriptive statistics. Percentages and frequencies were used for the categorical variables, while the mean ± standard deviation was calculated for the continuous variables.

Results

The characteristics of the patients are demonstrated in Table-1. The study involved 200 patients [97 (48.5%) male, 103 (51.5%) female] and the mean age was 42.56±17.49 years (range from 4 to 89). About half of the patients (44.8%) had a body mass index (BMI) of 25-29.5, and 26.5 % of them had a second disease in addition to COVID-19 and had a medication history. Sun exposure for less than 15 minutes/day had the highest percentage between the patients (39%) and the rest was equally divided between the patients with sun exposure from 15-30 minutes/day and the patients with sun exposure > 30 minutes/day.

Table 1. Patients' Characteristics

Variable	Category	Frequency (N)	Percentage (%)
Age (years)	4-30	58	29
	31-50	66	33
	51-70	52	26
	>70	24	12
Body mass index	18.5-24.9	43	22.2
	25-29.5	87	44.8
	30-34.5	49	25.3
	35-39.5	14	7.2
	>40	1	0.5
Comorbidities	No	147	73.5
	Yes	53	26.5
Medication history	No	147	73.5
	Yes	53	26.5
Diseases	Asthma	5	2.5
	COPD	4	2
	Heart failure	3	1.5
	Renal failure	1	0.5
	Hypertension	18	9
	Diabetes mellitus	14	7
	Cerebrovascular accident	2	1
	Myocardial infarction	1	0.5
	Anemia	1	0.5
	Arrhythmia	1	0.5
	Chronic bronchitis	1	0.5
	Hypothyroidism	1	0.5
	Sinusitis	1	0.5
	Left bundle branch block	1	0.5
	Rickets	1	0.5
	Chronic tonsillitis	1	0.5
Sun exposure (minutes/day)	<15	78	39
	15-30	59	29.5
	>30	63	31.5

Disease severity was classified according to signs and symptoms as: patient with no symptoms, mild to moderate, severe and critical cases (Figure 1) as mentioned in the patients methods section. The majority of patients (78%) had mild to moderate symptoms, and only 2.5% of them were asymptomatic. Patients with severe symptoms constituted 12.5% of patients sample while those with critical disease were only 7%.

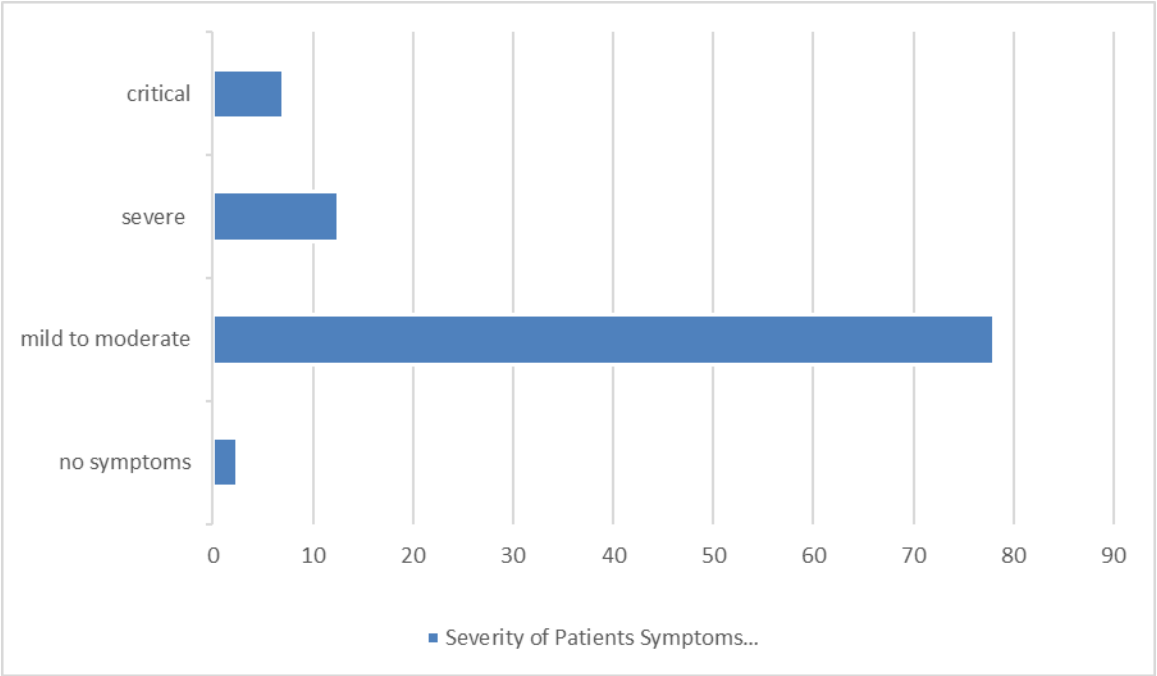

Figure 1. Severity of patients' symptoms.

Pharmacological protocols used by patients are shown in Table-2. Different therapies were used and all of them included vitamin D3. Other treatments used include: antipyretic (Paracetamol), antibiotics (either: Azithromycin, Levofloxacin, Meropenem, Metronidazole, Vancomycin, Teicoplanin, Amoxiclav, Ceftriaxone or Ceftazdime), antivirals (either: Oseltamivir, Favipiravir or Remidisver), anticoagulants (either: Enoxaparin or Rivaroxaban), steroids (either: Dexamethasone, Prednisolone or Hydrocortisone) and antimalarial (Hydroxychloroquine) and their frequencies and percentages are presented in Table-2.

Information about vitamin D dose and duration is prsented in Table-3. About half of the patients (51%) used vitamin D in a dose of 5,000-10,000 IU/day. Some patients used vitamin D as a single dose (9%), more than the half used it daily (55%) and the rest (36%) used it on weekly basis. Vitamin D was used for more than two weeks among less than half of the patients (44.5%) and some (6.3%) continued to use it even after recovery.

Table 2. Pharmacological protocols used for the patients.

No.			Medications	Frequency (N)	Percentage (%)
1			Vitamin D3 +vitamin C +zinc+ antipyretic	25	12.5
2			Vitamin D 3+vitamin C +zinc+ antibiotics	34	17
3			Vitamin D3+antibiotics +antiviral	18	9
4			Vitamin D3+ antibiotics +aspirin	13	6.5
5			Vitamin D3+vitamin C +zinc +Ivermectin	12	6
6			Vitamin D3+ antibiotics +antiviral +anticoagulant	13	6.5
7			Vitamin D3+ antibiotics +anticoagulant +steroids	9	4.5
8			Vitamin D3+antimalarial +antiviral	16	8
9			Vitamin D3+aspirin +Ivermectin	11	5.5
10			Vitamin D3+ antibiotics +antimalarial	14	7
11			Vitamin D3+antibiotic +steroids	17	8.5
12			Vitamin D3+ antimalarial +Ivermectin	10	5
13			Vitamin D3+antiviral +antibiotic +antimalarial +anticoagulant	8	4

Table3.Vitamin D3 dose and duration.

Patients	Dose (x 1000 IU)								
	Single			Daily		Weekly			
	10	200	300	< 5	5 - 10	≤ 10	15	30	50
No. (%)	4 (2)	5 (2.5)	9 (4.5)	8 (4)	102 (51)	5 (2.5)	6 (3)	9 (4.5)	52 (26)
	Duration								
	Single dose			1 – 2 weeks		> 2 weeks		Continuous	
No. (%)	18 (9)			80 (40)		89 (44.5)		13 (6.5)	

Table-4 shows the complications presented by the patients. Duration of symptoms for more than 10 days was experienced by about half of the patients (56%) and about the same percentage (56.6%) for those undergoing complication of the disease. The predominant complication was fatigue (20.5%) and there were rare symptoms of visual, rheumatologic, and hematological, reported in the study sample.

Table4. Complications of the patients.

Type of complication	**Frequency (N)**	**Percentage (%)**
Fatigue	**41**	**20.5**
Hair loss	**18**	**9**
Hormonal complications	**6**	**3**
Respiratory complications	**26**	**13**
Visual impairment	**2**	**1**
Reduce smell sensation*	**11**	**5.5**
Reduce taste sensation*	**6**	**3**
Gastrointestinal complications	**8**	**4**
Rheumatological complications	**5**	**2.5**
Cardiovascular complications	**8**	**4**
Metabolic complications	**11**	**5.5**
Hematological complications	**2**	**1**
Depression	**12**	**6**
Total	**113**	**56.5**

* Long standing complication after recovery

Discussion

Management of COVID-19 depends on the stage and severity of the disease, and since the virus replication is the highest before or soon after symptom appearance, antiviral medications are more effective when used early[29]. Hyperinflammation and coagulopathy are likely the cause of clinical complications. So, in later cases, anti-inflammatory, immune-modulators, anticoagulants, or combination of these treatments may be more effective than the antivirals. Although, there is no approved therapy for COVID-19, some medications have been shown to be beneficial[30].

The results of this study showed that male to female ratio was about 1:1, while in another study it was found to be about 2:1[31]. In most countries, data were reasonably similar, whereas in some countries the infection rate was higher in men than women[32]. However, the available data from previous studies provides differences in severity and death rate being a little higher in men versus women. This could be attributed to many reasons like higher smoking rate, suppression of immune response by testosterone, and higher rate of respiratory tract infection in male[32].

The highest rate of infected patients was found in age group ranging from 31-50 years. Usually younger patients showed less symptoms or may be asymptomatic[33]. Additionally, the lower number of older patients who participated in this study may explain this rate. Younger patients showed less susceptibility to infection due to high level of neutralizing antibodies, low levels of ACE-2 receptors in nasal epithelium, immature B and T cells and lower cytokines production, in contrast to that found in elderly patients which make them more susceptible to COVID-19[34]. The most prevalent comorbidities in this study sample were hypertension and diabetes mellitus seen in 9% and 7% of the patients respectively, while other comorbidities were distributed in lower percentages. A meta-analysis of six studies found that 17.1% of patients with COVID-19 were hypertensive, 16.4% had cardiac/cerebrovascular

disease, and 9.7% were diabetic. These comorbidities are risk factors for infection and bad prognosis[34].

Most of the patients had mild to moderate symptoms (78%) and few patients were asymptomatic while those with severe and critical symptoms were 12.5% and 7% respectively. According to the Iraqi national guidelines for management and treatment of COVID-19 released in August-September 2020, the initiation of a treatment depends on clinical presentation of the patients and clinical judgment by the doctors[35].

For mild cases, the treatment is mainly supportive with early starting with Favipiravir, while the use of other antivirals or antibiotics depends on the patient case. Moderate cases with manifestation of pneumonia required the early initiation of antiviral therapy (Favipiravir or Lobinavir/Ritonavir) with consideration for possible administration of supportive therapy, antibiotics, prophylactic anticoagulants, and plasma. Interferon and Ribavirin initiation depends on clinical judgment. Severe cases were managed by antiviral therapy of Remdesivir, Favipiravir or triple antiviral therapy (Lobinavir/ Ritonavir + Ribavirin+ interferon). Plasma therapy was considered at this stage and immuno-modulatory drug Tocilizumab can be used for cytokine storm. Empirical antibiotics, anticoagulant therapy and corticosteroid use should be well considered in severe cases. Critical cases required mechanical ventilation or evidence of cytokine storm. Critical cases managed as severe cases with ventilatory support and close monitoring[35].

Many different pharmacological protocols were used for treating the patients in the current study, in addition to supportive therapy (antipyretics, vitamin D, C and zinc). Antivirals were used in about half of the regimens since the majority of patients in the study sample had moderate infection. Oseltamivir is best initiated as early as possible and is useful in lowering the duration of fever when combined with antibacterial[36]. Favipiravir was included in the Iraqi guideline for the management and treatment of COVID-19 patients with mild disease even without the evidence of pneumonia. Results from a meta-analysis study showed clinical and radiological improvements but no significant differences on viral clearance, oxygen requirement and side effect profile from other antivirals, and additional clinical studies are required to give a definite judgment on whether the treatment with Favipiravir is the best option or not[37]. Remdesivir was considered as a promising agent for treating COVID-19 patients, as it further provides a new clinical insight into an efficient and adequate treatment for COVID-19 patients with the consideration of disease severity[38]. An Iraqi study emphasized that its early administration is accompanied with higher recovery rate, shorter residency in hospital and had a role in prevention of cytokine storm[39].

There were 48 patients using the antimalarial hydroxychloroquine. It was used as an off-label drug from the beginning of the pandemic due to its anti-inflammatory activity in addition to decreasing of lupus anticoagulant levels and platelet activation that is responsible for thrombotic events associated with COVID-19[40]. On the other hand, a meta-analysis study focused on its gastrointestinal, ophthalmic and cardiac adverse effects which may lead to treatment discontinuation[41]. "A strong recommendation against hydroxychloroquine for inpatients with COVID-19 of any severity" was included in the WHO living guidance on 31 March 2021[42].

Taking a deep look at the results, antibiotics were used by more than half of the patients (63%) with different antimicrobial agents have been prescribed. Extensive use of antibiotics could be due to the suspected bacterial pneumonia and evidence of super-infection that was accompanied with COVID-19[43]. However, inappropriate antibiotic prescribing can lead to bacterial resistance and other adverse effects. Similarly, inappropriate antibiotic prescription is highly associated with low age of patients, less disease severity, dry cough, bilateral interstitial infiltrates, and increased C reactive protein. Therefore, it is necessary to integrate an antibiotic use optimization program for COVID-19 patients [43].

Ivermectin was found in the treatment regimen of 33 patients in the current study despite that it is not included in the treatment protocol of COVID-19 patients in Iraq. It is an antiparasitic agent known from the 1970s and was discovered later to have an antiviral activity and was effective against certain Flavivirus and Chikungunya virus. Recently, it was assumed to be effective against coronavirus by inhibiting importin α/β mediated transport system of viral proteins demonstrated in vitro studies which lead to off-label use for COVID-19[44]. Some studies showed that it was associated significantly with lower COVID-19 deaths[45,46], especially in patients with severe pulmonary involvement [47]. However, the WHO living guideline on 31 March 2021 recommended its use only in the context of clinical trials, since there is little evidence about the effects of Ivermectin on mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance.

Data collected about vitamin D administration in the current study showed its unplanned use. This wide range of doses used should be taken into consideration and in required readjustment to meet the body needs and prevent toxicity from overdose. Vitamin D intake is recommended in many countries and the WHO

recommended a daily intake of 5 µg (200 IU) for adults but rising to15 µg (600 IU) over 65 years. An upper limit of 4000 IU /day in adults is relevant to European Food Standards Agency, UK Scientific Advisory Committee on Nutrition and US Institute of Medicine[48]. Older age, especially those with little sun exposure require a daily intake of 10–20 µg (400–800 IU /day) since they may have a lower response. It is critical to determine a baseline vitamin D status and target serum concentration to identify the appropriate supplementation dose [48]. Vitamin D level of >50 nmol/L is recommended by the US Institute of Medicine and achieved by 1000 IU/day dose and it is adequate even for obese individuals while it should be between 3000 - 4000 IU/day to achieve serum concentration of >75 nmol/L[49]. It was suggested that long-term exposure to doses of 25 µg (1000 IU) may be well tolerated, and higher exposures such as 45 µg (1800 IU) may be tolerated for short-term and under medical supervision, while a toxicity threshold of daily intakes ranges between 250 µg - 1000 µg ((10,000 IU- 40,000 IU)/day[50].

Vitamin D deficiency is a well-known global health problem and has negative impact on respiratory viral diseases such as COVID-19 in both children and adults. Vitamin D supplementation could potentially be effective in the treatment and prevention of COVID-19 particularly in those with risk factors and chronic diseases[51].The role of vitamin D in COVID-19 has been hypothesized since it may prevent acute respiratory infections (ARIs) by activating the innate and adaptive immune system, antioxidant activity and inhibition of renin-angiotensin system. These proposals lead to several randomized controlled trials trying to prove them but are still not convincing[50]. In this study, the results could not find a direct link between the dose of vitamin D and disease prognosis since it was not the sole therapy used, and the improvement in symptoms and recovery could be due to antiviral, immunomodulatory drug or other supportive therapy involved in the treatment protocol. Another explanation is the different regimen of vitamin D. Results from previous studies were ambiguous. Two meta-analysis studies found there were significant relations between vitamin D concentration and COVID-19 infection, severity and mortality [52,53]. In contrast, another meta-analysis that could not approve the association between vitamin D deficiency and greater COVID-19 severity reveal that no causal relationship has been tested until now and blood vitamin D levels had not been evaluated in COVID-19 patients [54].

The most predominant complication among the study sample was fatigue, respiratory complications and hair loss. More than half of the patients (56%) had symptoms for more than 10 days, which may reflect the same proportion of patients who experienced complications (56.5%). Some patients (even those who had mild versions of the disease) continue to experience symptoms after their initial recovery, and they may describe themselves as "long haulers" and the conditions have been called post-COVID-19 syndrome or "long COVID-19."[55]

By a variety of mechanisms, the lungs are the organs most affected in COVID-19[56], however non-respiratory complications have also been reported in the current study sample.

Conclusions

A wide, non-specific treatment protocols are used for the patients without compliance to the national guidance for management and treatment of COVID-19 patients in Iraq with administration of a wide range of pharmaceutical agents that usually requires monitoring for their safety and efficacy. Vitamin D administered in different doses and duration without depending on the basal serum concentration and after initiation of the treatment.

Limitation of the Study

Patients' vitamin D serum levels were not measured, while measuring them could be helpful to explain the wide range of doses used by the patients and to determine their true requirement to achieve better outcome and to overcome overdose administration. The evidence is currently inconsistent and insufficient due intensive care unit admission, inflammation, and pneumonia; further studies are required to evaluate the role of vitamin D supplements on treatment and management of COVID-19 patients.

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