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Effect of Vitamin D, C and Selenium Intake on Disease Severity and Outcomes in Patients COVID-19

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ABSTRACT

Background and purpose: COVID-19 is a viral respiratory disease that results in high mortality. Evidence suggests that micronutrients affect viral and bacterial infections. This study was performed to evaluate the effectiveness of micronutrients (vitamin D, vitamin C and selenium) on the disease severity in patients hospitalized with COVID-19.

Materials and methods: This retrospective cross-sectional study was carried out in patients with diagnosis of COVID-19 in Almahmodia Hospital, 2020. Medical records were reviewed and 42 were selected. Data of patients that received micronutrients including vitamin D, vitamin C and selenium and those that did not receive these supplements were compared. Duration of hospitalization, respiratory support, oxygen therapy, requiring invasive/non-invasive mechanical ventilation, and incident of death were investigated. Statistical analysis was done in SPSS V25.

Results: Survival rates in the groups receiving vitamin C, D and selenium were not significantly different from the groups that did not receive these supplements (P= 0.42, 0.63, 0.084, respectively). The study showed no significant relationship between vitamin D, C, and selenium intake and the need for ventilation due to respiratory distress (P= 0.139, 0.2 and 0.8, respectively).

Conclusion: No remarkable difference was seen between the recipients of vitamin C, D and selenium and those who did not receive supplements in terms of survival and the need for mechanical ventilation. So, these supplements did not affect the clinical outcomes of patients with COVID-19.

1. Introduction

Corona viruses are a large family of viruses that can cause disease in humans and many animal species such as camels, cats and bats. In rare cases, animal coronaviruses can infect humans, and then this virus can be transmitted between humans, like severe acute respiratory syndrome, middle east respiratory syndrome (SARS-COV) (CO-MERS) [1] in December 2019, an outbreak and epidemic. Epidemic of corona virus has been reported, which the World Health Organization [2] has named as NCOV-2019. All over the world from 1december 2019 to now (640,963,632) people were infected with this virus and (6,629,611) people died. The initial reports confirm person-to-person transmission during close contact with a person infected with the virus, and its transmission is like other types of coronaviruses through respiratory droplets, which are usually spread in the air by a person infected with the virus during coughing and sneezing, and on

surfaces and these contaminated respiratory droplets can be inhaled to the next person through contact with the nose or mouth into the lung. Therefore, if personal hygiene is not respected and hands are not washed frequently, the disease will be easily transmitted in crowded and crowded centers and areas [3]. It has not been transmitted from a healthy and asymptomatic person with a normal radiological test to another person [4]. Common symptoms of the disease include fever, cough, and shortness of breath. According to the CDC, the symptoms of the 2019 COVID-19 can be from 2 days to appear 14 days after the contact, and this is based on the data that was observed during the COV-MERS epidemic in the past [5].

In a study by Kakodkar and colleagues in April 2020, it was stated that daily or weekly administration of vitamin D in comparison with a monthly dose in reducing damage to alveolar cells in ARDS patients caused by viral and bacterial infection, especially in conditions of insufficient blood levels of this vitamin. It has a spectacular effect. Vitamin C plays a role in the function of phagocytes, the formation of T lymphocytes and the production of interferon, and previous studies have mentioned the role of vitamin C in reducing the severity and duration of seasonal colds and pneumonia and the development of ARDS [6, 7]. Also in the review article by Grant et al. stated in April 2020 that vitamin D can reduce the production of pro-inflammatory cytokines and reduce lung cell damage, and on the other hand, increase the immunity of the body's natural and acquired immune cells by inducing antimicrobial peptides such as 37-IL. 37-IL has extensive antimicrobial effects. It has effects on Gram-positive, Gram-negative bacteria, viruses with and without a protective envelope, and fungi. In in vitro and in vivo studies, vitamin D can reduce the vector version of rotaviruses [8]. Vitamin D by increasing the expression of glutathione reductase enzymes and Glutamate-cysteine ligase increases the production of glutathione, which, along with vitamin C and its antimicrobial activity, is recommended for the treatment of the Covid-19 virus. Dr. Frieden Tom from the Center for Disease Control and Prevention (CDC) stated on March 23, 2020 that the concentration of vitamin D in the body decreases with age, and this is evident in the increase in mortality following the infection of the Covid-19 virus with age [8]. In Li's study and his colleagues on August 9th , 2017 stated that the formulation of Seltamivir drug with selenium nanoparticles shows a very good antiviral effect with different mechanisms, including preventing MDCK cells from being infected by H1N1, preventing ROS production and activating p53 and akt [9]. Inflammatory drugs, including Corticosteroids, vitamins, micronutrients, and immune system modulating agents, have been used. Vitamin C or ascorbic acid is known for its anti-inflammatory and free radical scavenging properties [10 , 11]. It is also possible to synthesize vasopressors. and increase cortisol and affect the function of leukocytes through extracellular traps (NET), thereby strengthening immunity against various pathogens, including viruses [12,13]. Almost most of the countries in the world are affected by the Covid-19 virus, as well as the unavailability of definitive and transparent information regarding risk factors, mortality rates, and recovery rates. The rate of transmission, the type of behavior of the virus in certain populations such as the elderly, pregnant women, obese people, and doubts and ambiguity regarding the effectiveness of the drug treatments introduced against this virus, as well as the occurrence of various mutations and the risk of infection and various deaths with these viruses. Emerging, this study was designed with the aim of answering how to effectively add micronutrients such as vitamin C, vitamin D and selenium to the patients' medication regimen.

2. Materials and Methods

This research is a type of sectional-cross descriptive analytical study that evaluates the effectiveness of vitamin D, vitamin C and selenium micronutrients on the severity of the disease and outcomes of hospitalized patients with a definitive diagnosis of COVID-19 with moderate severity in Almahmodia Hospital from 2019 to 2020. The patients' information was recorded in the data collection form designed by the researchers of this study. According to the available

information, about 1500 patients were hospitalized in this center during this time period. Complete and with a definite diagnosis of the disease of COVID-19 based on clinical findings, the laboratory test that was admitted to the Almahmodia Hospital (which was considered as a referral center for coronavirus patients in Baghdad province during the outbreak of COVID-19) and received the micronutrients of vitamin D, vitamin C and selenium. patients with moderate severity of covid-19 were handcuffed in terms of receiving the supplements and the information of the patients receiving each The intake of two or three of these micronutrients was recorded and subjected to statistical analysis. Separate clustering was not done in terms of other drugs received and the underlying disease of the patients. The duration of hospitalization, the duration of respiratory support and the duration of oxygen therapy, the need for invasive/non-invasive mechanical ventilation and oxygen therapy and the occurrence of death in these patients were studied and evaluated based on the information recorded in their files.

2.1 Inclusion Criteria

Patients who were admitted to Almahmodia Hospital in Baghdad between 1/4/2019 to 31/6/2019 with a definite diagnosis of COVID-19 based on the isolation of the virus by the PCR RT method of swab samples from the throat, nasopharynx or oropharynx and tracheal secretions or typical radiological findings. They were. The severe criterion includes the number of breaths equal to or greater than 30 times per minute, arterial oxygen saturation less than 95 when the patient breathes in room air, severe multifocal lung involvement that increases by more than 50% within 48 hours, the patient's need for intubation and Mechanical Continuous positive airway pressure ventilation is bilevel positive airway pressure or (CPAP, BIPAP).

2.2 Exclusion Criteria

Patients whose files were incomplete or whose diagnosis was not confirmed. Data entry and analysis was done in SPSS version 25. Qualitative variables were described by number and percentage and quantitative variables were described by mean, standard deviation, median and quartile. In order to compare the quantitative variables, the independent sample t test was used and the qualitative variables, the Chi square test was used. In all cases, two-sided P value less than 0.05 was the criterion for judging statistical significance.

3. Results and Discussion

In this study, 42 cases of hospitalized patients diagnosed with covid-19 who received vitamin C, D and selenium supplements were examined, and 24% of patients received vitamin C, 24% of vitamin D and 8% of selenium. In table 1, the basic demographic information of the patients is shown.

Table 1: Basic information of patients at the time of admission

Variables	Number (percentage)	Median (first quartile, third quartile) Number (percentage)
Sex		
Woman	23 (54.8)	
Men	19 (45.2)	
Age (mean ± standard deviation)	52.9±14.5	54 (39.64)
Days of onset of symptoms (mean ± standard deviation)	6.8±3.5	7 (4.7)
Hospitalization days (mean ± standard deviation)	12.7 ±7.0	10 (7.19)
Days requiring mechanical ventilation	1.9±3.5	0 (0.4)

Dead people	13(30.9)	
Discharged people	29 (69.1)	
The first PCR test		
Negative	2(4.8)	
Positive	31 (73.8)	
Not reported	9 (21.4)	
Lung involvement	53.6 (13.8)	55(50.60)
Signs upon arrival:		
Cough	27 (64.3)	
Shortness of breath	30 (71.4)	
Chest pain	3 (7.1)	
Muscular pain	17 (40.5)	
Headache	11 (26.2)	
Diarrhea	9 (21.4)	
Tiredness	15 (35.7)	
abdominal pain	4 (9.5)	
joint's pain	1 (2.4)	
dizziness	5 (11.9)	
Fever	29 (69.1)	
nausea and vomiting	12 (28.6)	

The average age of patients was 52.9±14.5 years and 23% of patients were women. The most common symptoms observed in patients upon arrival included shortness of breath (30%), fever (29%), cough (27%), muscle pain (17%) and fatigue (15%). All patients had lung involvement at the time of admission and the average lung involvement of the examined patients was 13.8%. 73.8% of the studied patients had positive PCR at the time of admission. In these patients, 28.6% of cases required mechanical ventilation. According to the Kaplan-Meier diagram in figure 1, the probability of survival in patients receiving vitamin C was not statistically significantly different from the group that did not receive vitamin C (P=0.42). On the other hand, paying attention to figures 2 and 3, the probability of survival in the group receiving vitamin D and selenium was also not significantly different from the group that did not receive these supplements (P=0.08 and P=0.63), respectively as shown in table 2.

Table 2: Probability of survival in case of receiving or not receiving supplements

Group	Probability of survival 95%	Confidence interval	Meaningful level
Vitamin C recipient	0.15	0.45-0.01	0.42
Lack of vitamin C	0.71	0.91-0.31	
Vitamin D recipient	0.18	0.75-0.11	0.63
Lack of vitamin D	0.18	0.53-0.01	
Selenium receptor	0.14	0.98-0.3	0.084
Lack of selenium	0.27	0.53-0.07	

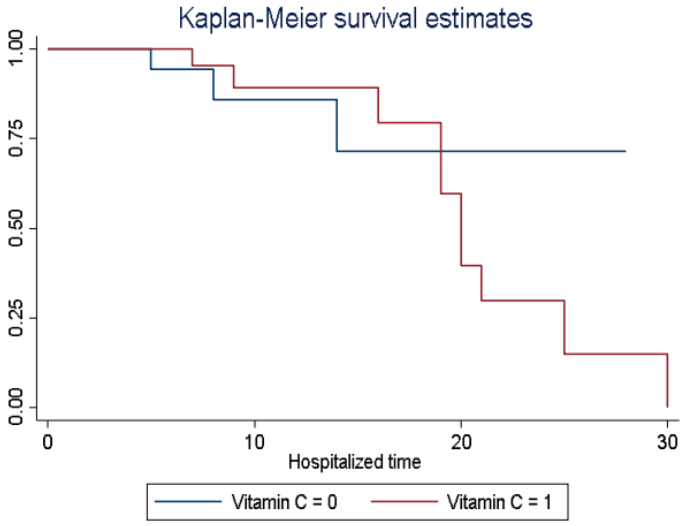

Figure 1: Kaplan-Meier diagram for the group receiving vitamin C (1) and the group not receiving vitamin C (0)

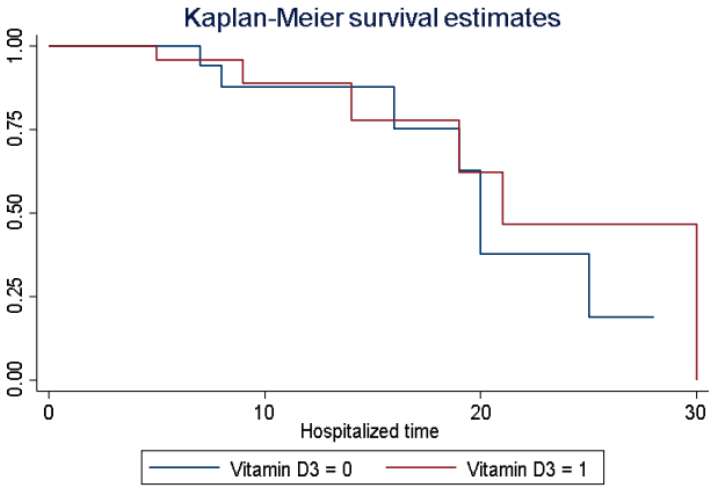

Figure 2: Kaplan-Meier chart for the group receiving vitamin D (1) and the group not receiving vitamin D (0)

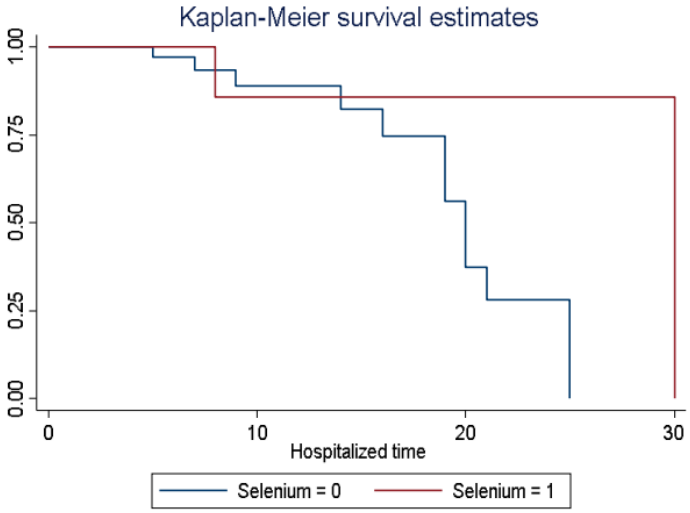

Figure 3: Kaplan-Meier diagram for the group receiving selenium (1) and the group not receiving selenium (0)

According to table 3, there was a significant relationship between the experience of mechanical ventilation and death due to covid-19. The relative frequency of death in patients with ventilation is significantly higher. In other words, 85 percent of deaths occur in patients with ventilation (P=0.00).

Table 3: Mortality rates in patients requiring mechanical ventilation and those who did not require mechanical ventilation

Group	Discharged persons Number (percentage)	Dead persons Number (percentage)	Total Number (percentage)
Persons who need mechanical ventilation	1 (3.45)	11 (84.62)	12 (28.57)
Persons who did not need mechanical ventilation	28 (96.55)	2 (15.38)	30 (71.43)

In table 4, it can be seen that the relationship between vitamin C intake and death due to covid-19 was not significant. In other words, the difference between the relative frequency of death in patients receiving vitamin C and the relative frequency of death in patients without receiving vitamin C is not significant, and this observed difference is random (P=0.08).

Table 4: Comparison of the number of deaths in the group receiving and not receiving vitamin C

Group	Discharged persons Number (percentage)	Dead persons Number (percentage)	Total Number (percentage)
Vitamin C recipient	14 (48.28)	10 (76.92)	24 (57.14)
Lack of vitamin C	15 (51.72)	3 (23.08)	18 (42.86)

As can be seen in table 5, the relationship between receiving vitamin D and death from covid-19 is not significant, in other words, the difference between the relative frequency of death in patients receiving vitamin D (46%) and the relative frequency of death in patients without receiving vitamin D is not significant (54%). And this observed difference is accidental. (P = 0.33)

Table 5: Number of deaths in two groups receiving and not receiving vitamin D

Group	Discharged persons Number (percentage)	Dead persons Number (percentage)	Total Number (percentage)
Vitamin D recipient	18 (62.07)	6 (46.15)	24 (57.14)
Lack of vitamin D	11 (37.93)	7 (53.85)	18 (42.86)

Table 6 shows the relationship between receiving selenium and death due to covid-19, but this relationship was not significant. In other words, the difference in the relative frequency of death in patients receiving selenium (15.4%) is not significant with the relative frequency of death in patients without selenium (85%) and this observed difference is random (P = 0.686).

Table 6: Number of deaths in two groups receiving and not receiving selenium

Group	Discharged persons Number (percentage)	Dead persons Number (percentage)	Total Number (percentage)
Selenium receptor	6 (20.69)	2 (15.38)	8 (19.05)
Lack of selenium	23 (79.31)	11 (84.62)	34 (80.95)

Table 7 examines the relationship between receiving supplements and the experience of ventilation due to COVID-19 and this relationship was not significant for any of the supplements. In other words, the difference between the relative frequency of ventilation experience with vitamin C, D and selenium intake and the relative frequency of ventilation experience in patients without receiving supplements is not significant and this observed difference is random.

Table 7: Comparison of the need for mechanical ventilation in patients receiving C, D and selenium supplements

Group		Need for mechanical ventilation number (percentage)	No need for mechanical ventilation Number (percentage)	Total number (percentage)	Significance level
Vitamin C	Recived	9 (75)	15 (50)	24 (57.14)	0.139
	No recived	3 (25)	15 (50)	18 (42.86)	
Vitamin D	Recived	5 (41.67)	19 (63.33)	24 (57.14)	0.2
	No recived	7 (58.33)	11 (58.33)	18 (42.86)	
Selenium	Recived	2 (16.67)	6 (20)	8 (19.05)	0.804
	No recived	10 (83.33)	24 (80)	34 (80.95)	

4. Conclusion

The purpose of this study is to evaluate the effects of micronutrients (vitamin D, vitamin C and selenium) on the severity of the disease and the outcomes of hospitalized patients diagnosed with covid-19 in the Almahmodia Hospital of Baghdad from July to September 2019, including 42 cases. Out of 1500 files of hospitalized patients in this period of time who received these vitamins were reviewed based on the inclusion criteria. Vitamin C along with Corticosteroids and Thiamine reduces the risk of progressive dysfunction of organs including injury. Renal severity and mortality reduction in patients with severe sepsis and septic shock are related [14,15], but the evidence seems to be contradictory, because the published randomized trial did not show any significant clinical benefit [16]. A systematic and meta-analysis that was published in 2022, 26 studies including 5633 patients with COVID receiving vitamin C, D and zinc supplements were examined. In the examination between the groups, receiving vitamin C and D had no effect on the mortality rate of the patients. [17]. On the other hand, it has been reported that vitamin C can increase the level of antiviral cytokines (such as β/α-IFN) and the formation of free radicals, and as a result, reduce the viral load and inflammatory response. Vitamin C is an important supplement in the protection vital cells against the damage related to the production of 18 ROS (Reactive oxygen species), there is a need for detailed clinical trial studies to confirm the effects of vitamin C. In line with the findings of this study, the study carried out by Tos T. Davoudi et al., in Almahmodia Hospital, Baghdad, after measuring the serum level of vitamin D before admission to the hospital, the results of vitamin D evaluation as an indicator of the consequences of COVID-19 infection did not support it [19]. The studies conducted based on the Kaplan-Meier diagram and no significant correlation was observed between the data, the use of vitamin C, D and selenium supplements did not have an effect on the survival rate of hospitalized patients infected with COVID-19. Also, in terms of the need for mechanical ventilation, there was no significant difference between the groups receiving micronutrients and the control group. This shows that the irrational prescription of these micronutrients will not have a significant effect on reducing the severity of the disease or the clinical outcome of hospitalized patients infected with COVID-19. It is suggested that in future studies, in order to find clearer effects of these micronutrients, clinical trials should be conducted by equating the

received dose of micronutrients in the control and sample groups. It is also suggested to use higher doses of vitamin C in future studies. Measuring the serum level of vitamin D3 should be used to improve the frequency of administration according to the level of deficiency in each patient and to reduce lung cell damage following cytokine storm [6 , 8].

On the other hand, this retrospective study was conducted at a time when no specific and unique treatment was known to control the disease of COVID-19, therefore, this can make the prediction and deterioration of the disease and the process of improvement of the patients a problem, and the optimal time to start nutritional supplements affect this study, because in the case of many drugs such as antivirals and anti-inflammatories, their administration at the right time from the onset of symptoms has been effective in the prognosis of patients.

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