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Electrolytes, Zinc and Vitamin D_3 in COVID-19 Patients with Cardiovascular Complications

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Abstract

Introduction. COVID-19 is strongly linked to cardiovascular disease, with direct myocardial injury and systemic inflammation as common mechanisms. Pre-existing or infection-induced cardiovascular disease worsens the outcomes for COVID-19 patients.

Materials and methods. To estimate the serum electrolytes (Na^+, K^+, Ca^{++}, Zn) and vitamin D_3, the study depended on ichroma ii device for Vitamin D_3 and Chemistry Analyzer for electrolytes in patient samples.

Results. A study was conducted on 192 individuals diagnosed with COVID-19, including 35 critical cases, 53 severe cases, 54 moderate cases, and 50 individuals in a control group. The age group with the highest prevalence of infection was between 50–69 years, while the lowest prevalence was observed in those under 30 years. The study found significant decreases in calcium, potassium, sodium, zinc, and vitamin D_3 levels among COVID-19 patients compared to the control group. Zinc and vitamin D_3 levels showed a significant correlation with sex, with males experiencing a decline in zinc levels and females having lower vitamin D_3 levels. The concentration of calcium, sodium, and zinc showed a negative correlation with age, with older patients having the lowest levels. COVID-19 patients with chronic cardiac issues and high blood pressure exhibited the lowest levels of these markers. The severity of the disease also had a detrimental impact on electrolyte levels, zinc, and vitamin D_3, with critical cases showing the lowest levels. The complications such as heart failure were associated with lower levels of potassium, sodium, and zinc.

Conclusion. In conclusion, the study revealed significant associations between COVID-19 and decreased electrolyte levels, zinc, and vitamin D_3. Sex and age were found to be correlated with these markers. Patients with chronic cardiac issues and high blood pressure exhibited the lowest levels of these markers. The severity of the disease was also linked to lower electrolyte levels, zinc, and vitamin D_3. Complications such as heart failure were associated with decreased levels of potassium, sodium, and zinc.

Keywords: *COVID-19; Cardiovascular; Vitamin D_3; Zinc; electrolyte*

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
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Электролиты, цинк и витамин D_3 у пациентов с COVID-19 с сердечно-сосудистыми осложнениями

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Резюме

Введение. COVID-19 тесно связан с сердечно-сосудистыми заболеваниями, общими механизмами которых являются прямое повреждение миокарда и системное воспаление. Ранее существовавшие или вызванные инфекцией сердечно-сосудистые заболевания ухудшают исходы для пациентов с COVID-19.

Материалы и методы. В образцах сыворотки крови пациентов проводили количественное определение электролитов (Na^+, K^+, Ca^{++}, Zn) с помощью биохимического анализатора и витамина D_3 с помощью устройства ichroma ii.

Результаты. В исследовании приняли участие 142 пациента с диагнозом COVID-19, включая 35 критических случаев, 53 тяжелых случая, 54 среднетяжелых случая, а также 50 человек в контрольной группе. Возрастная группа с наибольшей распространенностью инфекции составила 50–69 лет, а наименьшая распространенность наблюдалась среди лиц моложе 30 лет. Исследование выявило значительное снижение уровней кальция, калия, натрия, цинка и витамина D_3 среди пациентов с COVID-19 по сравнению с контрольной группой. Уровни цинка и витамина D_3 продемонстрировали значительную корреляцию с полом: у мужчин наблюдалось снижение уровня цинка, а у женщин – более низкий уровень витамина D_3. Концентрация кальция, натрия и цинка имела отрицательную корреляцию с возрастом, при этом у пожилых пациентов наблюдалась самая низкая концентрация. У пациентов с COVID-19 с хроническими заболеваниями сердца и высоким кровяным давлением наблюдались самые низкие уровни этих маркеров. Тяжесть заболевания также оказывала пагубное влияние на уровень электролитов, цинка и витамина D_3, при этом в критических случаях COVID-19 наблюдались самые низкие уровни. Такие осложнения, как сердечная недостаточность, были связаны с более низким уровнем калия, натрия и цинка.

Вывод. Исследование выявило значительную связь между COVID-19 и снижением уровней электролитов, цинка и витамина D_3. Было обнаружено, что пол и возраст коррелируют с этими маркерами. У пациентов с хроническими сердечно-сосудистыми заболеваниями и высоким кровяным давлением наблюдались самые низкие уровни этих маркеров. Тяжесть заболевания COVID-19 также была связана с более низким уровнем электролитов, цинка и витамина D_3. Такие осложнения, как сердечная недостаточность, были связаны со снижением уровней калия, натрия и цинка.

Ключевые слова: *COVID-19; сердечно-сосудистые заболевания; витамин D_3; цинк; электролиты*

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Этическое утверждение. Исследование проводилось при добровольном информированном согласии пациентов. Протокол исследования одобрен этическим комитетом факультета биологии Научного колледжа Университета Ти-Кара (Протокол №. 22 от 02.05.2021).

Introduction

Global Coronavirus Disease 2019 (COVID-19), commonly known as severe acute respiratory syndrome 2, is a serious disease caused by coronavirus SARS-CoV-2, affecting the lives of all people in the world. Several previous studies have shown that SARS-CoV-2 is similar in many biological features to SARS-CoV, including the way it enters host cells, by binding to a spike protein with angiotensin-converting enzyme 2 (ACE2) [1]. SARS-CoV is an animal virus that caused the outbreak of severe acute respiratory syndrome in 2002 [2]. COVID-19 infection can lead to long-term difficulties due to many physiological factors, however the specific processes behind these consequences are still not fully understood. SARS-CoV-2 has both a direct and indirect pathogenic impact. Given that the virus depends on ACE2 for infecting the target cell, and as previously stated, ACE2 is present in numerous cells through-

out the body, the virus will directly impact the organs it invades [3, 4]. The virus can directly harm organs that contain cells with the ACE2 enzyme, such as the respiratory system, heart, blood vessels, pancreas, and others, leading to long-term consequences. Furthermore, the indirect impact of infection may be attributed to several factors such as immune system dysfunction, acute infections, blood coagulation, hypoxia, and acid-base imbalance. Additionally, it is worth noting the adverse psychological impacts experienced by the patient [5].

Several clinical studies have reported an association between COVID-19 and cardiovascular disease. Patients with pre-existing chronic cardiovascular disease appear to be closely associated with a worse outcome and an increased risk of dying with COVID-19 [6]. Also, COVID-19 can cause cardiovascular problems including acute coronary syndrome, arrhythmias, venous thromboembolism, and others. This is done through the host cell receptors of the virus, ACE2, which is found in the cells of the heart and blood vessels [7]. Therefore, COVID-19 can exacerbate underlying cardiovascular conditions and even precipitate new heart complications. Mechanistically, the interaction between S protein and ACE2 plays a major role in pathogenesis, particularly in cardiovascular manifestations [8]. Potential interactions between infection with COVID-19, comorbid cardiovascular disease, and medications are of serious concern [9].

Material and method

Study Design

The study was carried out in the Al-Hussein Teaching Hospital, the Nasiriyah Heart Center, and several isolation centers in Thi-Qar Governorate. It was a case-control study that was done at the hospital level. To obtain total of 192 blood samples from patients with 50 as control sample, a basic random sample method was employed. Arterial and venous blood samples were obtained from both COVID-19 patients and the control group in the following manner: Approximately seven milliliters of each sample were taken and then split into two parts. Initially, a volume of 6 ml was transferred into a gel tube and allowed to stand at room temperature for roughly 30 minutes. The remaining portion was transferred to an EDTA tube. The gel tubes were subjected to centrifugation at a speed of 4000 revolutions per minute for a duration of 5 minutes. The resulting serum sample was divided into three separate portions, each containing approximately 500 µl, and stored in deep freeze at a temperature of −20 °C. Blood samples in the EDTA tube were promptly utilized for the determination of complete blood counts after thorough mixing. The serum separated was used for the estimation of Serum electrolytes (Na^+, K^+, Ca^{++}, Zn) by using ichroma ii device for Vitamin D_3 and Chemistry Analyze for electrolytes.

Ethics

The research protocol was approved by the Ethics Committee of the Institution Department of Biology, College of Science, University of Thi-Qar (Protocol No. 22 dated 2/5/2021).

Criteria for Selection and Exclusion

This research project includes individuals who have been diagnosed with COVID-19 and were admitted to Imam Hussein Teaching Hospital, Nasiriyah Heart Center, and some isolation centers in Thi-Qar Governorate, of both sexes and the age up to > 69 years. Patients who did not provide a sufficient sample and the patients whose data we could not obtain well were excluded from the study.

Statistical Analysis

Version 26 of the Statistical Package for the Social Sciences (SPSS) was utilized to conduct the statistical analysis. To compare the groups statistically, independent sample T test for mean comparison between patients and control group and one way ANOVA for mean comparison between groups were employed.

Results

Descriptive of Data Study

This study focuses on individuals diagnosed with COVID-19 and encompasses a total of 192 samples. These samples are categorized based on the degree of the infection, with 35 instances classified as critical, 53 cases as severe and 54 cases as moderate and 50 samples serving as a control group. **Figure 1** illustrates the distribution of samples.

Figure 2 illustrates the distribution of COVID-19 patients in this study based on their age and gender. The age group with the highest prevalence of COVID infection among both males and females is between 50–69 years, whereas the age group with the lowest prevalence is under 30 years.

Imbalances in Electrolytes, Zinc, and Vitamin D_3 in Patients

The findings of the present investigation indicate an imbalance in the concentrations of calcium, potassium, sodium, zinc, and vitamin D_3 among those affected by COVID-19. Patients exhibited a significant decrease in all of these indicators compared to the control group, with a significance level of < 0.05. **Table 1** displays this information.

Electrolytes, Zinc, and Vitamin D_3 in patient by gender

The findings presented in **Table 2** indicate a statistically significant correlation, with a significance level of > 0.05, between sex and the levels of zinc and vitamin D_3 in COVID-19 patients. However, no significant differences associated with gender were recorded in this study for the electrolyte group. Males exibited the most significant decline in zinc levels, whereas females have lower levels of vitamin D_3 compared to males.

Association of Patients' Age with Low Electrolytes, Zinc and Vitamin D_3 during COVID-19 Infection

The present study demonstrated a notable negative correlation between the age of individuals with COVID-19 and their concentrations of calcium, sodium, and zinc, with statistical significance at a level below 0.05. The group of

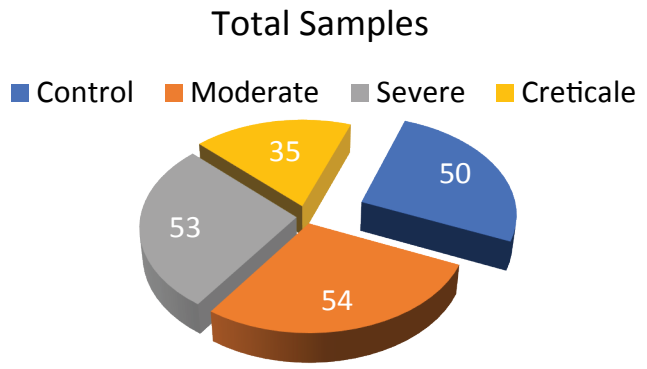

Fig. 1. Distribution of all study samples, including those from patients and the control group.

Рис. 1. Распределение исследовавшихся образцов от пациентов и контрольной группы.

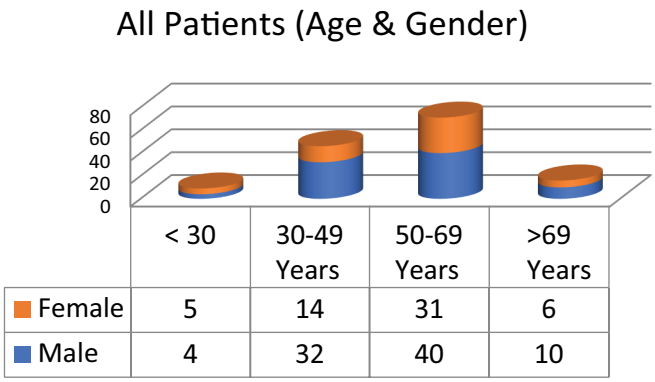

Fig. 2. The distribution of COVID-19 patients by age and gender.

Рис. 2. Распределение пациентов с COVID-19 по возрасту и полу.

Table 1. Calcium, Potassium, Sodium, Zinc and Vitamin D_3 in COVID-19 patients and control group

Таблица 1. Уровни кальция, калия, натрия, цинка и витамина D_3 у пациентов с COVID-19 и в контрольной группе

Parameters	Mean ± standard deviation		T-test Value
	Control	Patients	
Ca^+	9.620 ± 0.324	8.660 ± 1.574	0.045
K^+	4.537 ± 0.446	3.370 ± 0.712	< 0.001
Na^+	140.3 ± 10.83	137.1 ± 17.52	0.004
Zn	110.0 ± 16.39	90.3 ± 24.049	< 0.001
VD_3	24.28 ± 6.057	14.70 ± 5.406	< 0.001

Table 2. Electrolytes, zinc, and vitamin D_3 in COVID-19 patients by gender

Таблица 2. Уровни электролитов, цинка и витамина D_3 у пациентов с COVID-19 в зависимости от пола

Parameters	Mean ± standard deviation		T-test Value
	Male	Female	
Ca^+	8.691 ± 1.631	8.619 ± 1.497	0.791
K^+	3.583 ± 0.709	3.274 ± 0.924	0.097
Na^+	136.4 ± 9.812	138.3 ± 7.787	0.132
Zn	85.69 ± 25.10	97.54 ± 20.53	0.004
VD_3	16.79 ± 5.211	11.60 ± 4.048	< 0.001

patients above the age of 69 years had the lowest levels of these markers. The detailed data are shown in **Table 3**.

The Effect of Chronic Diseases on the Levels of Electrolytes, Zinc, and Vitamin D_3 in COVID-19 Patients

Chronic disorders have a substantial impact on the values of some parameters documented in **Table 4**. The present findings demonstrated statistically significant variations at a significance level of < 0.05 for calcium, potassium, sodium, zinc, and vitamin D_3 among patients based on their chronic illnesses. COVID-19 patients with pre-existing conditions of chronic cardiac issues and chronic high blood pressure exhibited the lowest levels of these measures. The highest level was found in patients without any chronic illnesses.

Correlation between the Severity of COVID-19 Infection and the Levels of Electrolytes, Zinc, and Vitamin D_3

The findings of the present study, as presented in **Table 5**, indicate that the severity of the disease has a detrimental impact on the levels of electrolytes, zinc, and vitamin D_3. The group of patients with critical conditions exhibited the lowest levels for all of these parameters, in contrast to those with moderate or severe cases. These results are statistically significant at level of less than 0.05.

Electrolyte, Zinc and Vitamin D_3 Levels According to Disease Complications Resulting from COVID-19 Infection

The current results showed a significant variation in the levels of potassium, sodium, and zinc in COVID-19 patients depending on the disease complications resulting

Table 3. Electrolytes, zinc and vitamin D_3 in COVID-19 patients by age
Таблица 3. Уровни электролитов, цинка и витамина D_3 у пациентов с COVID-19 в зависимости от возраста

Age Groups Parameters		Mean & Std.	ANOVA Sig.	LSD Sig.
Ca^+	< 30 Years	10.92 ± 1.620	< 0.001	$0.018^{1,2}$, $0.001^{1,3}$, $0.001^{1,4}$, $0.006^{2,3}$, $0.001^{2,4}$, $0.001^{3,4,}$
	30–49 Years	8.843 ± 1.417		
	50–69 Years	8.177 ± 1.385		
	> 69 Years	6.180 ± 1.257		
K^+	< 30 Years	3.435 ± 0.275	0.143	$NS^{1,2}$, $NS^{1,3}$, $NS^{1,4}$, $N^{2,3}$, $NS^{2,4}$, $NS^{3,4}$
	30–49 Years	3.564 ± 0.704		
	50–69 Years	3.284 ± 0.738		
	> 69 Years	3.104 ± 0.721		
Na^+	< 30 Years	141.2 ± 13.30	0.002	$NS^{1,2}$, $NS^{1,3}$, $0.001^{1,4}$, $NS^{2,3}$, $0.001^{2,4}$, $0.001^{3,4}$
	30–49 Years	137.8 ± 6.747		
	50–69 Years	137.6 ± 16.12		
	> 69 Years	131.0 ± 12.74		
Zn	< 30 Years	109.6 ± 8.688	0.001	$NS^{1,2}$, $0.003^{1,3}$, $0.006^{1,4}$, $0.005^{2,3}$, $0.029^{2,4}$, $NS^{3,4}$
	30–49 Years	97.46 ± 19.35		
	50–69 Years	85.04 ± 26.00		
	> 69 Years	82.76 ± 24.04		
VD_3	< 30 Years	15.51 ± 3.407	0.318	$NS^{1,2}$, $NS^{1,3}$, $NS^{1,4}$, $NS^{2,3}$, $NS^{2,4}$, $NS^{3,4}$
	30–49 Years	15.28 ± 5.323		
	50–69 Years	13.04 ± 5.829		
	> 69 Years	12.81 ± 4.246		

Table 4. Electrolytes, zinc and vitamin D_3 in COVID-19 patients by chronic diseases
Таблица 4. Уровни электролитов, цинка и витамина D_3 у пациентов с COVID-19 в зависимости от хронических заболеваний

Chronic Disease Parameters		Mean & Std.	ANOVA Sig.	LSD Sig.
Ca^+	Non	9.932 ± 1.591	0.054	$0.024^{1,2}$, $NS^{1,3}$,$NS^{1,4}$, $NS^{1,5}$, $NS^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $NS^{3,4}$, $NS^{3,5}$, $NS^{4,5}$
	HBP	7.042 ± 1.551		
	DM	8.925 ± 1.285		
	Heart problems	8.762 ± 1.381		
	Mix	8.808 ± 1.404		
K^+	Non	3.691 ± 0.668	<0.001	$0.001^{1,2}$, $NS^{1,3}$,$0.001^{1,4}$, $0.001^{1,5}$, $0.001^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $0.001^{3,4}$, $0.001^{3,5}$, $NS^{4,5}$
	HBP	3.091 ± 0.649		
	DM	3.442 ± 1.193		
	Heart problems	3.063 ± 0.611		
	Mix	3.098 ± 0.925		
Na^+	Non	139.6 ± 6.291	0.001	$0.016^{1,2}$, $NS^{1,3}$,$0.008^{1,4}$, $NS^{1,5}$, $0.025^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $0.016^{3,4}$, $NS^{3,5}$, $0.016^{4,5}$
	HBP	132.5 ± 6.960		
	DM	137.3 ± 11.23		
	Heart problems	131.3 ± 12.54		
	Mix	137.8 ± 11.02		
Zn	Non	94.10 ± 22.32	<0.001	$0.018^{1,2}$, $NS^{1,3}$,$0.003^{1,4}$, $NS^{1,5}$, $NS^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $NS^{3,4}$, $NS^{3,5}$, $NS^{4,5}$
	HBP	75.60 ± 21.97		
	DM	86.22 ± 22.91		
	Heart problems	69.90 ± 23.86		
	Mix	80.54 ± 37.05		
VD_3	Non	17.54 ± 5.286	0.008	$NS^{1,2}$, $NS^{1,3}$, $0.012^{1,4}$, $NS^{1,5}$, $NS^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $NS^{3,4}$, $NS^{3,5}$, $NS^{4,5}$
	HBP	14.78 ± 6.037		
	DM	14.90 ± 6.301		
	Heart problems	12.12 ± 4.764		
	Mix	15.71 ± 5.589		

Table 5. Electrolytes, zinc and vitamin D_3 in COVID-19 patients by the severity of infection
Таблица 5. Уровни электролитов, цинка и витамина D_3 у пациентов с COVID-19 в зависимости от тяжести инфекции

Severity Parameters		Mean & Std.	ANOVA Sig.	LSD Sig.
Ca^+	Moderate	8.338 ± 1.461	0.048	$NS^{1,2}$, $0.001^{1,3}$, $0.001^{2,3}$
	Severe	8.169 ± 1.524		
	Critical	7.857 ± 1.577		
K^+	Moderate	3.497 ± 0.719	NS	$NS^{1,2}$, $NS^{1,3}$, $NS^{2,3}$
	Severe	3.338 ± 0.625		
	Critical	3.264 ± 0.815		
Na^+	Moderate	138.9 ± 5.896	0.001	$NS^{1,2}$, $0.010^{1,3}$, $NS^{2,3}$
	Severe	136.5 ± 6.485		
	Critical	135.3 ± 10.35		
Zn	Moderate	109.0 ± 10.98	<0.001	$0.001^{1,2}$, $0.001^{1,3}$, $0.001^{2,3}$
	Severe	85.28 ± 21.61		
	Critical	69.28 ± 21.09		
VD_3	Moderate	15.35 ± 5.366	<0.001	$NS^{1,2}$, $NS^{1,3}$, $NS^{2,3}$
	Severe	14.39 ± 4.932		
	Critical	12.37 ± 3,536		

from it, at a level of statistical significance < 0.05. The lowest level of these parameters was recorded in COVID-19 patients who developed heart failure as an outcome of the infection, as shown in **Table 6**.

Discussion

Perhaps more than any other infectious disease, COVID-19 has captured the attention of cardiologists because of its clear association with cardiovascular disease. Direct myocardial injury due to viral involvement of cardiomyocytes and the effect of systemic inflammation appear to be the most common mechanisms responsible for cardiac injury [10, 11]. The presence of pre-existing and/or infection-induced cardiovascular disease has been consistently shown to be associated with a significantly worse outcome in COVID-19 patients [12].

The current study included 142 people with COVID-19 infection and 50 samples as a control group (192 total samples). Infections were distributed among patients according to gender, and the percentage of male patients infected with COVID-19 was 60.6%, while 39.4% were females. The results of the current study are in agreement with most previous studies, including the study by Su et al. [13]. It differs from the results of a study Al-Hijaj et al. [14] in Basra, which recorded a higher infection rate among females instead of males. Moreover, the study Mukherjee and Bahan [15] stated that even if the infection rate was equal between males and females, the infection would be more severe and dangerous in males. Among the most important factors that lead to an increase in infection among males compared to females, are hormonal factors, as scientific research confirms that sex hormones contribute to increasing males' susceptibility to infection with COVID-19 [16]. It is believed that the presence of ACE2 receptors in testicular tissue in men increases the likelihood of exposure to the virus and the development of infection [17]. Social and professional factors play a major role in increasing infection in males, as males are exposed to the virus, such as work that requires physical presence and interaction with others. In addition, men may have a higher proportion of social gatherings that expose them to the risk of infection than women [18]. It should be noted that these factors vary according to the cultural, social, and demographic context of each region.

Depending on age, the current study recorded that the age group ranging from 50 to 69 years includes the largest number of COVID-19 patients, their percentage to the total study population being 50%, and their infection is more serious. Meanwhile, the lowest percentage of patients is 6.3% within the age group less than 35 years. This result is consistent with Mushtaq et al. [19], and differs with Davies et al. [20], which stated that the most common detection of COVID cases is in age groups under 50 years old, because they are more socially active, which increases the chances of exposure to the virus. The high rate of infection in advanced age groups, as shown in the results of the current study, may be attributed to several important factors, including the immune system and chronic diseases [21]. Older people may have an immune system that is less able to fight infection and thus increases the likelihood of developing serious symptoms resulting from infection. Moreover, the presence of underlying medical conditions such as respiratory diseases, diabetes, and cardiovascular disease can increase the risk of infection.

COVID-19 patients were divided in this study based on the severity of the disease, and among them were 54 moderate cases, 53 severe cases, and 35 critical

Table 6. The relationship between electrolytes, zinc and vitamin D_3 in COVID-19 patients and the disease complications
Таблица 6. Взаимосвязь между уровнями электролитов, цинка и витамина D_3 у пациентов с COVID-19 и осложнениями заболевания

Complication Parameters		Mean & Std.	ANOVA Sig.	LSD Sig.
Ca^+	Non	8.993 ± 1.581	NS	$NS^{1,2}$, $NS^{1,3}$, $NS^{1,4}$, $NS^{1,5}$, $NS^{1,6}$, $NS^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $NS^{2,6}$, $NS^{3,4}$, $NS^{3,5}$, $NS^{3,6}$, $NS^{4,5}$, $NS^{4,6}$, $NS^{5,6}$
	MI	8.662 ± 1.364		
	HF	8.400 ± 1.104		
	Arrhythmia	8.783 ± 2.319		
	PE	8.350 ± 1.034		
	MIX	8.060 ± 2.617		
K^+	Non	3.400 ± 0.731	0.002	$NS^{1,2}$, $NS^{1,3}$, $0.018^{1,4}$, $NS^{1,5}$, $NS^{1,6}$, $NS^{2,3}$, $0.006^{2,4}$, $NS^{2,5}$, $NS^{2,6}$, $NS^{3,4}$, $NS^{3,5}$, $NS^{3,6}$, $0.012^{4,5}$, $0.024^{4,6}$, $NS^{5,6}$
	MI	3.953 ± 0.528		
	HF	3.060 ± 0.282		
	Arrhythmia	2.393 ± 0.344		
	PE	3.555 ± 0.967		
	MIX	3.302 ± 0.791		
Na^+	Non	139.8 ± 7.118	0.003	$NS^{1,2}$, $0.006^{1,3}$, $NS^{1,4}$, $NS^{1,5}$, $0.034^{1,6}$, $NS^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $NS^{2,6}$, $NS^{3,4}$, $NS^{3,5}$, $NS^{3,6}$, $NS^{4,5}$, $NS^{4,6}$, $NS^{5,6}$
	MI	137.2 ± 8.972		
	HF	132.0 ± 2.000		
	Arrhythmia	136.0 ± 2.190		
	PE	138.2 ± 6.751		
	MIX	135.0 ± 15.82		
Zn	Non	95.08 ± 21.62	<0.001	$0.030^{1,2}$, $0.002^{1,3}$, $0.024^{1,4}$, $0.010^{1,5}$, $0.006^{1,6}$, $NS^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $NS^{2,6}$, $NS^{3,4}$, $NS^{3,5}$, $NS^{3,6}$, $NS^{4,5}$, $NS^{4,6}$, $NS^{5,6}$
	MI	77.40 ± 24.01		
	HF	66.25 ± 38.60		
	Arrhythmia	75.16 ± 15.83		
	PE	69.25 ± 29.74		
	MIX	67.84 ± 21.19		
VD_3	Non	16.75 ± 5.442	NS	$NS^{1,2}$, $NS^{1,3}$, $NS^{1,4}$, $NS^{1,5}$, $NS^{1,6}$, $NS^{2,3}$, $NS^{2,4}$, $NS^{2,5}$, $NS^{2,6}$, $NS^{3,4}$, $NS^{3,5}$, $NS^{3,6}$, $NS^{4,5}$, $NS^{4,6}$, $NS^{5,6}$
	MI	14.87 ± 6.895		
	HF	13.50 ± 4.203		
	Arrhythmia	15.33 ± 5.573		
	PE	14.00 ± 1.414		
	MIX	13.40 ± 5.594		

cases (38%, 37.3%, 24.7%, respectively), and there was no statistically significant relationship between them. This may be since these samples were collected in isolation centers, and that most COVID-19 patients who have a mild or moderate infection do not visit hospitals, as do severe and critical cases that require immediate intervention due to shortness of breath and lack of oxygen, as well as severe inflammatory symptoms resulting from their infection. Of course, the percentages of severity of COVID-19 infection vary in different countries, due to many factors such as the health policies, the health care system, circulating strains, the level of vaccination, and demographic factors [22].

According to a study Elham et al. [23], there is a clear decrease in the levels of calcium, potassium, sodium, zinc, and vitamin D_3 in COVID-19 patients, and this was proven by the results of the current study when comparing these parameters in COVID-19 patients compared to the control group. Calcium plays a critical role in supporting both cellular and humoral immunity, and there is widespread recognition of an increased risk of respiratory virus-related illness in individuals with a low calcium intake, compared to those with a normal calcium intake [24]. Potassium is the most abundant cation within cells with its share approximately 98%. It has several important functions, including transmitting electrical impulses in the heart, acid-base regulation, and fluid balance, and is essential for muscle and nerve function [25]. Blood potassium imbalance results in adverse complications including muscle weakness and arrhythmia [26]. Important causes of hypokalemia in these patients include malnutri-

tion due to anorexia, decreased intake of potassium-rich foods including fruits and vegetables, diarrhea and vomiting due to illness, and of course increased potassium loss due to diuretic therapy [27]. Some medications used to treat COVID-19, such as azithromycin and hydroxymeloroquine, lead to hypokalemia. Hyperaldosterism caused by activation of the renin-angiotensin system stimulates the release of potassium through urine [28].

As for the causes of hyponatremia, this may be due to the loss of sodium in the urine [29]. Severe hyponatremia has significant associated morbidity and mortality and is a well-known complication of water intoxication, especially in older patients with an impaired thirst mechanism who are advised to increase fluid intake during chronic illness. Subsequently, all patients were counselled regarding fluid intake, and specific advice was given regarding symptoms that may represent water intoxication, where sodium monitoring on a more frequent than routine basis may be warranted. Although we cannot be certain of the cause of increased urinary sodium loss, it is possible that it represents a stress response, due to increased levels of urinary catecholamine's, heart dysfunction, resulting in hypervolemia and sodium deficiency [30].

Zinc deficiency in COVID-19 patients is due to respiratory infection depleting zinc in the body, as it is consumed in the inflammation and healing processes. In addition to malnutrition caused by anorexia, severe stress leads to high levels of some proteins that cause zinc consumption [31]. It is reported that high body temperatures in COVID-19 patients lead to loss of zinc through sweating [32]. Inflammatory stress often causes a negative zinc balance by utilizing plasma zinc and causing the release of zinc from liver mineral-bound protein aggregates into the plasma. Although zinc has different effects, it plays an important role in the immune system. Zinc deficiency may lead to weakened immunity and increased risk of infection. Zinc also has anti-inflammatory effects and reduces cytokine production [31]. In these findings, as patients had decreased zinc levels, zinc was released from cells to rescue inflammatory stress that may have persisted over the course of cytokine generation. Given these findings and effects, zinc is an essential mineral to prevent the progression and worsening of COVID-19 infection. Low vitamin D_3 has negative consequences for COVID-19 patients. Its low level may occur in patients due to malnutrition and psychological stress, in addition to calcium deficiency, which plays an important role in the absorption of vitamin D_3 [33]. There is no doubt that lack of exposure to ultraviolet rays from sunlight, which stimulates the synthesis of vitamin D3, causes the decrease.

The current study found a clear significant difference in the levels of zinc and vitamin D_3 depending on the gender of the patients, as the level of zinc decreased more in males than in females, and this is consistent with what was mentioned in the study by Maares et al. [34], where male gender is considered a risk factor. On the contrary, a greater decrease in vitamin D_3 was recorded in females compared to males with COVID-19 infection. This result is consistent with a study [35]. Environmental influences and smoking may have a negative effect on zinc levels in males. While the decrease in vitamin D_3 in females is greater than in males, perhaps due to lack of activity and exposure to sunlight compared to males, as well as due to some medical factors such as digestive disorders and malabsorption [36].

Calcium, sodium, and zinc all have a significant negative relationship with the age of patients infected with COVID-19, as the results of the current study demonstrated a greater decrease in these parameters as age increases. These results are consistent with the study by Elham et al. [23]. The reason may be due to disturbances in the digestive system associated with aging, and thus its efficiency in absorbing these minerals decreases [37]. In addition, older adults take some different medications that negatively affect the balance of minerals in the body, such as blood pressure medications and diuretics. Also, hormonal changes in the elderly, such as a deficiency in the hormone parathormone, which regulates calcium levels, lead to its imbalance in the blood [38].

The results of the current study demonstrated that the levels of potassium, sodium, zinc, and vitamin D_3 are affected by the presence of chronic diseases in COVID-19 patients. The greatest decrease in these parameters was recorded in patients with a history of heart problems, chronic high blood pressure, and diabetes. This result is consistent with a study by Severino et al. [39], which reported a relationship between potassium, sodium, zinc, D_3, and heart problems. It is known and proven in the current study that the level of B-type natriuretic peptide (BNP) increases in patients with critical and severe conditions, as well as in the presence or occurrence of cardiovascular complications, which causes a decrease in the levels of calcium and sodium because of their excretion through the urine [40]. Moreover, liver and kidney functions decline with age, and thus the absorption of vitamin D_3 decreases, which leads to a disturbance in the level of minerals, especially calcium. As the severity of COVID-19 infection in patients increases, these parameters decrease further [41], which is literally consistent with the results of the current study.

Changes in the level of minerals within the cells promote the activation of inflammatory pathways. Calcium plays an important role in many important functions including the blood clotting process. Calcium deficiency affects the function of the heart, as it leads to decreased contraction in the left ventricle, because the flow of calcium into the cell is primarily responsible for the initiation and extent of heart contraction. This results in fibrillation, atrial flutter, and arrhythmia [42]. Potassium has a role in the functioning of the heart, as a decrease in it causes irregular heartbeat, as happens with a calcium deficiency, which leads to a prolongation of the QT interval. Pulmonary arterial thrombosis is caused by arrhythmia caused by potassium deficiency during COVID-19 infection [43]. Hyponatremia leads to greater activation of the RAAS system, starting a vicious cycle. It also causes congestive heart failure and atrial fibrillation [44]. Some studies indicate a disturbance in the functioning of the hormone vasopressin, which regulates and controls the amount of water that is filtered from the kidneys. IL-6 as-

sociated with COVID-19 infection could be a cause of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) caused by cytokine release or due to lung tissue and alveolar cell injury that induces SIADH via hypoxic pulmonary vasoconstriction [45]. Therefore, low sodium could be an indicator of respiratory failure.

Zinc has antiviral properties, as it inhibits the synthesis of viral RNA and prevents its replication. It prevents the interaction of the viral S protein with ACE2 and thus reduces the severity of the infection [46]. Zinc binds to RNA-dependent RNA polymerase causing inhibition of elongation and reduced binding of the viral mRNA template [47]. Low zinc impairs lymphoid tissue development and reduces natural killer cell function, thus impairing innate immunity. Its decrease is also linked to macrophage activation and cytokine generation [48]. There is a relationship between low zinc and cardiovascular disease because its presence reduces ROS, which, when elevated, causes oxidative stress, which is a cause of cardiovascular disease, as it causes activation of inflammatory pathways and stimulation of cytokines and enzymes associated with inflammation [49]. There are 24 zinc transporters in the heart, so any disturbance in the level of zinc causes cardiovascular diseases such as the development of arterial hypertension as well as coronary heart disease, and its deficiency causes thickening of the walls of blood vessels [50]. Serum zinc levels can be an indicator for the diagnosis of acute myocardial infarction [51].

Vitamin D_3 deficiency leads to many heart problems, including heart arrhythmia, heart failure, and sometimes clotting [52]. Myocardium contains vitamin D_3 receptors and has anti-hypertrophic effects and regulates calcium influx and thus increases myocardial contractility. Therefore, congestive heart failure occurs in cases of vitamin D_3 deficiency [53]. Its receptors are also found throughout the blood vessels, where it has an important role in preventing atherosclerosis and the occurrence of blood clots because it stimulates the production of endothelial nitric oxide, downregulates pro-coagulant tissue factors, and promotes vascular repair [54]. Therefore, cardiovascular problems such as high blood pressure and blood clotting occur in COVID-19 patients who suffer from a deficiency in the level of vitamin D_3. Vitamin D_3 reduces the severity of COVID-19 infection, as it directly suppresses the transcription of the renin gene, thus dilating blood vessels.

Conclusion

In conclusion, the study revealed significant associations between COVID-19 and decreased levels of calcium, potassium, sodium, zinc, and vitamin D_3. Sex and age were found to be correlated with these markers, with males experiencing a decline in zinc levels and older patients having the lowest concentrations of calcium, sodium, and zinc. Patients with chronic cardiac issues and high blood pressure exhibited the lowest levels of these markers. The severity of the disease was also linked to lower electrolyte levels, zinc, and vitamin D_3, with critical cases showing the most significant decline. Complications such as heart failure were associated with decreased levels of potassium, sodium, and zinc.

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