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Effects of COVID-19 on Plasma Sodium and Potassium Levels in Adult Patients

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ABSTRACT: **BACKGROUND**: Novel coronavirus (SARS-CoV-2) infects human lung tissue cells through angiotensin-converting enzyme-2 (ACE2), and the body's sodium is an important factor for regulating the expression of ACE2. Through this study, we found that low blood sodium is significantly associated with SARS-CoV-2 infection. OBJECTIVE: Assess the incidence of Na and K in newly diagnosed COVID-10 infected patients without a previous history of diseases. Study the correlation between age and sex. **PATIENTS AND METHODS**: A prospective cohort study that involved a recently newly diagnosed COVID-infected patient. Each patient was followed up prospectively for the duration of admission (two weeks), and random plasma Na and K was recorded for each patient at diagnosis, during the active infection (7-10 days from admission). The study was carried out in the Baghdad Teaching Medical City complex outpatient clinic. The study started in April 2021 and was completed in June 2021 (about three months). **RESULTS**: The study included 60 patients, with a mean age of 45.9 ± 18.6 years, with a similar male-to-female ratio. Patients were negative for past medical and surgical history **.**There was a significant change in blood Na levels in older than younger patients compared to normal values. No change has been found in K levels compared to normal levels of the reference range. **CONCLUSIONS**: There is an increased risk of hyponatremia in apparently normal newly diagnosed COVID-19 patients, which is more prevalent in males older than younger or female patients.

Keywords: Novel Coronavirus (Sars-Cov-2); Plasma Sodium and Potassium Levels; and Adult Patients.

INTRODUCTION

On December 31, 2019, the China Health Authority informed the World Health Organization (WHO) of several cases of pneumonia of an unknown cause in Wuhan City, situated in Hubei Province, central China [Lu, H. *et al*., 2020; Hui, D. S. *et al*., 2020]. The cases were first reported on December 8, 2019. Many patients worked at or resided nearby the close-by Huanan Seafood Wholesale Market. However, other early cases had no relationship to this market. SARS-CoV-2 belongs to the Coronavirus family and the Nidovirales order. The family had two subfamilies, mainly Coronavirus and Torovirinae, having the members corresponding to the subfamily Coronavirus. SARS-CoV-2 is regarded to be a recently found Beta coronavirus which has the capacity to infect humans. [Gorbalenya, A. E. *et al*., 2020]. SARS-CoV-2 infection usually occurs in adult males, having the median age of those affected being between 34 to 59 years. SARS-CoV-2 has an increased tendency to infect individuals who have chronic comorbidities, which include cardiovascular and cerebrovascular diseases and also diabetes. [Burki, T. K, 2020 – Chen, N. *et al*., 2020]. The highest rate of severe instances happens in people around 60 years or older, as well as in those who have certain medical conditions, including cardiovascular cerebrovascular diseases as well as diabetes. [Wan, Y. *et al*., 2020 – Totura, A. L. *et al*., 2012]. The host range of a virus is established by several molecular interactions, including interactions with receptors. The receptor binding domain of the envelope spike (S) proteins of SARS-CoV-2 was shown to have a structural affinity with that of SARS-COVID despite variations in amino acid composition at some important locations. [Hamming, I. *et al*., 2004; Patel, A. *et al*., 2020; Harapan, H. *et al*., 2020; Huang, J. Q. *et al*., 1996; Chung, M. *et al*., 2020; Hu, W. *et al*., 2021]. Additional comprehensive structural analysis provides strong evidence that SARS-CoV-2 is likely to utilize the host receptor angiotensin-converting enzyme 2 (ACE2) to get into cells. This is the same receptor that facilitates the infection of the airway epithelium as well as alveolar type 2 (AT2) pneumocytes by SARS-CoV, which are pulmonary cells who are synthesizing pulmonary surfactant. However, the recognition of receptors is not the sole factor that decides species specificity. Upon connecting to their specific receptor, SARS-CoV-2 promptly infiltrates host cells, where it enters in contact with the innate immune system's reaction. The radiographic observations can vary based on the age of the patient, the progress of the disease, the immune state, the existence in other medical conditions, and the initial therapy. [Wang, D. *et al*., 2020;

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Kuhn, J. H. *et al*., 2004; Zhu, N. *et al*., 2020]. A research detailing 41 of the early instances of 2019-nCoV infection found that all 41 patients had pneumonia, as seen by aberrant results upon chest computed tomography (CT scan). Administering pharmacologic prophylaxis for venous thromboembolism to all patients hospitalized with COVID-19 is a crucial aspect of their therapy, in line with recommendations from many expert societies. Multiple studies indicate a significant incidence of thromboembolic consequences in hospitalized patients having COVID-19, especially those in severe conditions [Payen, D. *et al*., 2008; Ford, H. *et al*., 2001]. The goal of this study is to examine the sodium and potassium levels in COVID-19 patients who are admitted to the hospital. Additionally, the study wants to determine if there are any differences in these electrolyte levels between young and senior patients, as well as any variations related to gender.

2. METHODS

2.1. Study Design

A prospective cohort study that involved a recently newly diagnosed COVID-infected patient (reverse transcriptase polymerase chain reaction, RT-PCR confirmed) the diagnosis based on recent Iraqi guidelines in 2021. Each patient was followed up prospectively for the duration of admission (approximately two weeks or more), and random plasma sodium/potassium was performed for each patient at diagnosis (*Test 1*), during the active infection, and 7-10 days after hospitalization while on therapy (*Test 2*).

2.2. Study Setting

The study was carried out in the Baghdad Teaching Medical City complex hospitalized patients. The study started in January 2021 and was completed in March 2021 (about three months).

2.2.1. Inclusion Criteria

- Newly diagnosed COVID with negative past medical-surgical medication history.
- Age above 18 years.

2.2.2. Exclusion Criteria

- Patients with any past medical or surgical history
- Patients with a history of malignancy
- Pregnant women
- Use of any medication before COVID-19 infection.

2.3. Measured Variables

Patients' age, gender, family history of diseases, past medical history, drug use during admission, and random plasma sodium and potassium were taken.

2.3.1. Sodium/Potassium Normal Range:

The abnormal levels of both potassium and sodium are tabulated below with associated clinical features **(Table 2.1 and 2.2).**

Table 2.1: Reference range plasma sodium and clinical features

Classification	Serum Sodium	Features
Mild hyponatremia	130 – 134	Mostly asymptomatic but can report/ present with headache, nausea, vomiting, fatigue, confusion, anorexia, and muscle cramps.
Moderate hyponatremia	125 - 129	Gait disturbances, headache, vomiting, fatigue, confusion, muscle cramps, and depressed deep tendon reflexes.
Severe hyponatremia	< 120	Delirium, restlessness, agitation or lethargy, seizures, brainstem herniation, respiratory arrest, coma, and death

Table 2.2: Normal and abnormal range of potassium and associated diseases

Classification	Potassium level, (mM = mEq/L)	Symptoms
Normal	3.5 – 5 mM	Asymptomatic
Mild hypokalemia	3 – 3.5 mM	Asymptomatic
Moderate hypokalemia	2.5 – 3 Mm	May cause mild symptoms - Intestinal smooth muscle dysfunction causes ileus.
Severe hypokalemia	< 2.5 mM	May cause severe symptoms - Muscle cramps - Weakness (classically ascending weakness, can involve diaphragm) - Torsades de pointes, other arrhythmias - Heart failure - Rhabdomyolysis

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2.4. Statistical Analysis

Data were expressed as the mean ± standard deviation. Comparisons between the investigated parameters for control and patient groups were conducted using the t-test. $P < 0.05$ was considered a statistically significant difference. Statistical results were obtained using GraphPad Prism 5.0 (GraphPad Software Inc., La Jolla, CA, USA). The histogram chart was designed using the Microsoft Office 2010 Excel program.

3. RESULTS

3.1. Variation of Age and Gender of Studied Groups:

A total of 60 patients were enrolled in the present study. Their demographic parameters are approximately matched, with a mean age of 45.9 ± 12 (range, 24-70 years). The gender distribution was matched, as you can see in **Table 3.1.**

Table 3.1: Results of demographic parameters

Groups	Age
Total (n=60)	45.9 ± 18.6
Female (n=29)	49.8 ±8.8
Male (n=31)	45 ± 10.7
>50 years (n=27)	66.5±7.3
<50 years (n=33)	41.7±5.2

3.2. Total Sodium-Potassium Level in COVID-19 Patients

The plasma concentration (mmol/L) of sodium and potassium were determined in COVID-19 hospitalized patients over the two-time period with 7-10 days intervals between test 1 and test 2, while the patients were on therapy of COVID-19 dependent protocols. The results confirmed that sodium concentration (135.6±5) was close to the lowest acceptable limit of the normal range. Moreover, the plasma concentration of potassium (4.4±0.6) stands close to the lowest acceptable limit of the normal range (**Figure 1).** A non-significant ($p<0.05$) differences exist between test 1 and test 2 for both studied parameters: sodium and potassium. Cases included in our study were all either normal or mild, according to **Table 2.1** and **Table 2.2,** respectively.

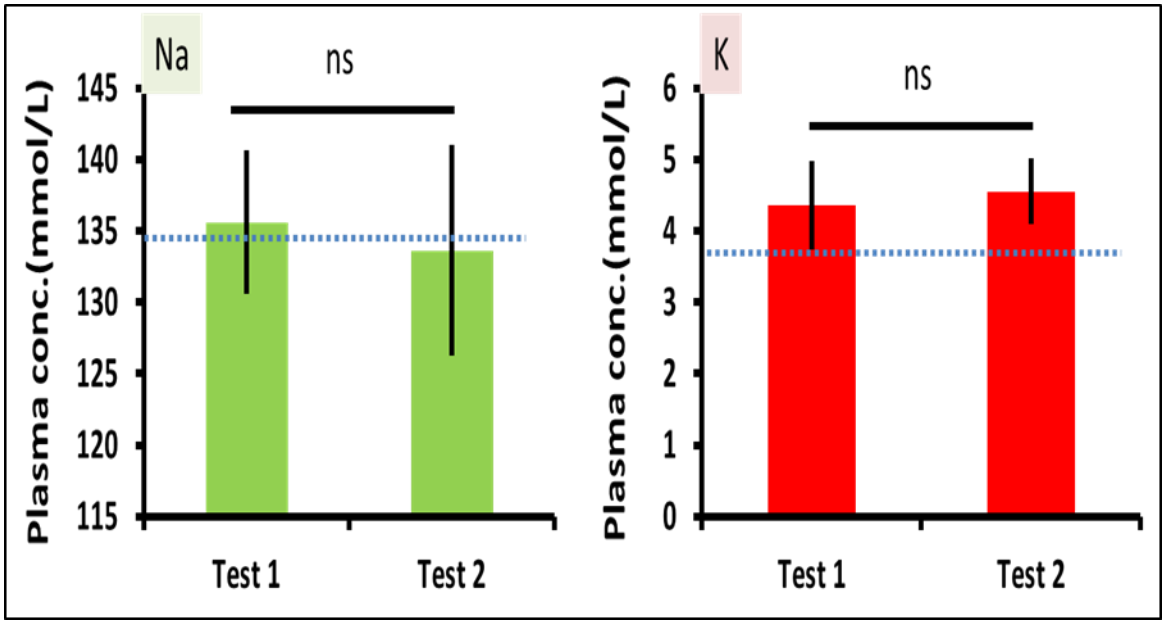

Figure 3.1: The plasma concentration of sodium and potassium in COVID-19 patients over two repeats with 7-10 days intervals in between. Test 1=upon admission, Test 2=after 7-10 days following therapy. The results are presented as mean ± SD, K=potassium, Na=Sodium, ns=non-significant, and dotted line=lowest limit of the acceptable plasma concentration range.

3.3. Sex-Variation and Sodium/Potassium Levels:

The result confirmed that the concentration (mmol/L) of sodium is associated with sex. When the concentration average was determined for males and females separately, the study has found that plasma sodium concentration was significantly reduced in males (133±5.5) compared to females

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(137±3.2). However, potassium has no link to sex because the plasma concentrations were similar between males (4.4±0.6) and females (4.2±0.5), with non-significant differences were found between them (**Figure 3.2**).

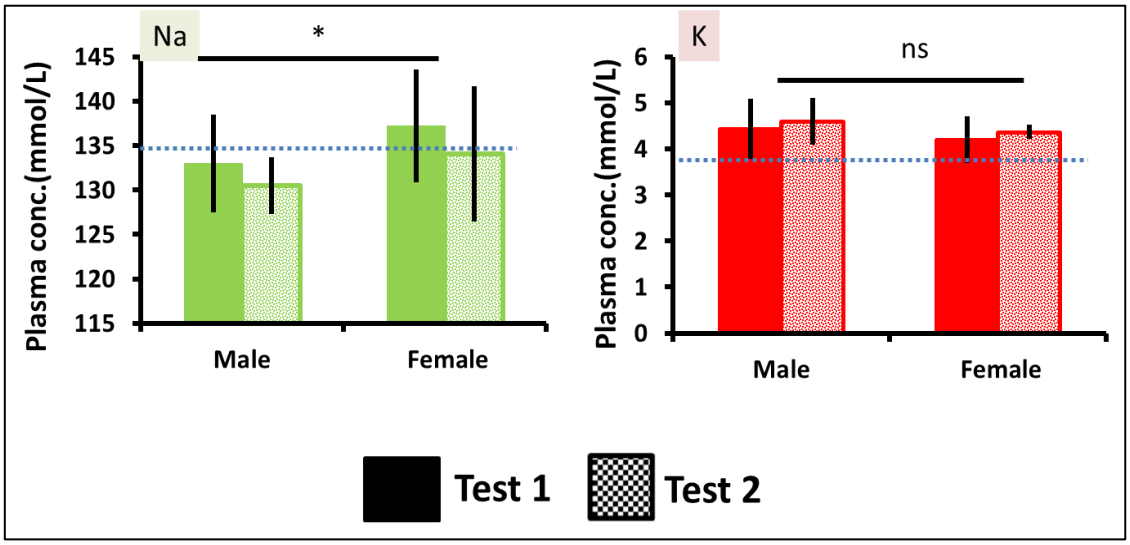

Figure 3.2: Sex variation in the plasma concentration of sodium and potassium in COVID-19 patients over two repeats with 7-10 days intervals in between. Test 1=upon admission, Test 2=after 7-10 days following therapy. The results are presented as mean ± SD, K=potassium, Na=Sodium, ns=non-significant, and dotted line=lowest acceptable plasma concentration of sodium and potassium.

3.4. Age-Variation and Sodium/Potassium levels:

Similarly, the result confirmed that the concentration (mmol/L) of sodium is associated with age. When the concentration average were determined for >50 years subject versus those <50 years separately, the study has found that plasma sodium concentration were significantly reduced in the elder [131.3±5.5 and 131.2±5.2; test1 and test 2, respectively] compared to younger [138.4±2.1 and 136.7±8.9; test1 and test 2, respectively], however, potassium has no link to sex because the plasma concentrations were similar between elder [4.3±0.6 and 4.7±0.4; test1 and test 2, respectively] and younger [4.4±0.6 and 4.5±0.5; test1 and test 2, respectively] with a non-significant ($p > 0.05$)differences were found between them (**Figure 3.3).**

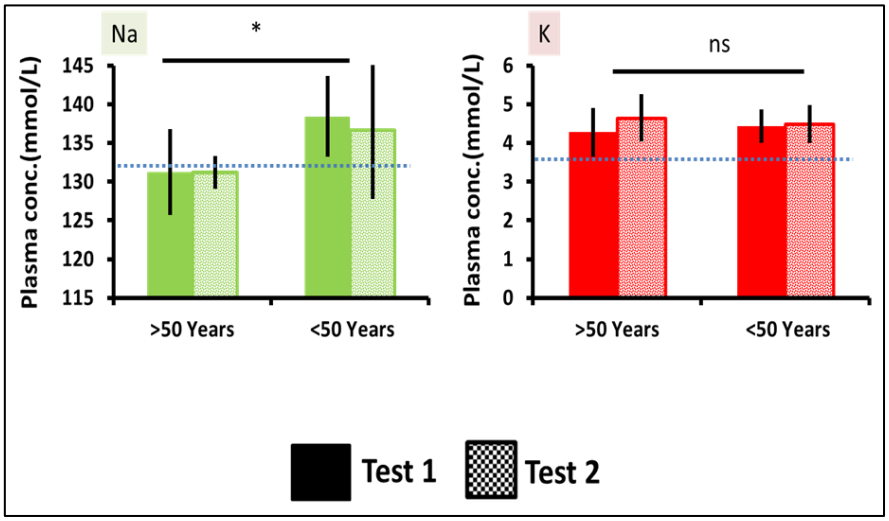

Figure 3.3: Age-based variation in the plasma concentration of sodium and potassium in COVID-19 patients over two repeats with 7-10 days intervals in between. Test 1=upon admission, Test 2=after 7-10 days following therapy. The results are presented as mean ± SD, K=potassium, Na=Sodium, ns=non-significant, and dotted line=lowest acceptable plasma concentration of sodium and potassium.

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DISCUSSION

Several clinical and histological investigations have shown evidence of low levels of potassium (hypokalemia), low levels of sodium (hyponatremia), syndrome of inappropriate antidiuretic hormone secretion (SIADH), incomplete Fanconi syndrome, as well as tubulopathy in people infected with SARS-CoV-2 [Sakr, Y. *et al*., 2005] Both the data from China and the information gathered from SARS-COV case series strongly support the need to closely monitor electrolyte levels of patients who are infected with SARS-CoV-2 [Bouchard, J. *et al*., 2009]. In order to draw clear conclusions with regard to this clinical consequence, it is essential to replicate this clinical observation at numerous healthcare facilities. However, the present study demonstrated that COVID-19-infected patients show a slight non-significant change in potassium and sodium levels when compared to the normal range despite of slight reduction in the level in overall patients since potassium and sodium levels are close to the lowest limit of the normal range. Moreover, we did confirm that old age (>50) and male patients were more at risk of hyponatremia and hypokalemia [Cao, Y. *et al*., 2020 – Pourfridoni, M. *et al*., 2021].

In the present study, potassium levels were within acceptable normal range with no differences between sex or age, however, still the level is at the lowest acceptable limit. Therefore, healthcare providers should be aware about the potassium levels. Potassium levels <3.0 mmol/l can be arrhythmogenic and specifically can cause QTc interval prolongation, torsade de pointes, ventricular fibrillation, and sudden cardiac death. Induction of arrhythmias can be due to multi-factorial aetiologies of cardiac injury in SARS-CoV-2 patients, such as hypoxia-mediated, direct tissue damage, cytokine-storm syndrome, worsening coronary perfusion, and the direct effects of medications. Both of these factors really emphasize the importance of maintaining normokalaemia in these patients to reduce morbidity and mortality. [Tinawi, M, 2020 – Sahoo, S. *et al*., 2016]

In addition to the arrhythmogenic effects of both the SARS-CoV-2 cardiac sequelae and various clinical trial drugs, many patients are being given diuretics to improve the oxygenation in ARDS, which also risks hypokalemic complications. Loop diuretics can induce hypokalemia by blocking the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) in the thick ascending limb of the loop of Henle, which results in failure of sodium, potassium, and chloride to be reabsorbed into the concentrated medullary interstitium (this transporter normally reabsorbs about 25% of the sodium load) [Lindestam, U. *et al*., 2020; Cryan, P. M. *et al*., 2013; Luo, Y. *et al*., 2020]. This enhances distal tubular concentration of sodium, reduced hypertonicity of the surrounding interstitial and less water reabsorption in the collecting duct. Distal sodium delivery increases potassium loss via the Na^+/K^+-ATPase pumps at the apical membrane of the principal cell of the collecting duct, as there is more sodium to be exchanged with potassium for excretion. Thiazide diuretics can cause hypokalaemia by the same principle of enhanced distal sodium delivery as they block the sodium-chloride co-symporter (NCC) in the distal convoluted tubule.

Furthermore, loop diuretics also block NKCC2 at the macula densa, which (along with the RAS-activation response to initial volume reduction) induces renin secretion, making RAS system measurement inaccurate if patients are on diuretics. If diuretics are to be used, it would be wise to consider potassium-sparing agents in hypokalaemic patients to reduce the cardiac complications of worsening hypokalemia that can occur with those that are not potassium-sparing. [Pourfridoni, M. *et al*., 2021 – Skogestad, J. *et al*., 2018]

Hyponatremia is closely related to the incidence and severity of community-acquired pneumonia and perforated acute appendicitis in children. Clinical studies have shown that the elderly are more susceptible to SARS-CoV-2 infection and become more severe than the young and middle-aged people [Lindestam, U. *et al*., 2020 - Luo, Y. *et al*., 2014], which may be due to the lower blood sodium levels in the elderly population [Wrotek, A . *et al*., 2014]. One of the reasons may be the decrease of the regulation mechanism of sodium ions in the elderly, including the decrease of renal reabsorption function for sodium ions during the aging process; however, another key reason may be the result of a long-term low sodium diet. For a long time, especially in developed countries, the strategy of low sodium diet being actively implemented by physicians, medical organizations, and public health agencies has played an important role in preventing and controlling hypertension and related diseases. However, some recent evidence suggests that very low sodium intake may actually have adverse effects on human health, which may also preset a very unfavorable

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state in certain populations against SARS-CoV-2 infection [Giannis, D. *et al*., 2020]. In this study, we found that some young, severe patients with CODIV-19 had serious hyponatremia, reinforcing our interpretations. In addition, the low susceptibility of SARS-CoV-2 infection to minors suggests that the relatively high levels of blood sodium may play a role in fighting against the virus infection. Whether an age-dependent change in blood sodium levels is related to increasing expression of ACE2 in human tissue cells, in particular in alveolar cells, remains to be experimentally confirmed.

Our study clearly confirmed that COVID-19 patients shown non-significant hyponatremia (sodium level stands close to the lowest acceptable limit), and we confirmed that elderly males is more susceptible to hyponatremia than the young or female group. Therefore, care should be taken to avoid this risk factor, which might participate in a further increase in the rate of mortality, especially in the elderly. The presence of a high concentration of extracellular sodium ions in lower aquatic organisms, even reaching to 440 mmol/L in squid, may be a natural means for them to fight against various microbial infections besides the realization of physiological functions such as nerve action potential [Lindestam, U. *et al*., 2020]. The blood sodium concentration with an average level of 146.0 mmol/L in bats that can coexist with multiple coronaviruses in vivo is indeed much higher than that in human beings. In addition, it was found that North American bat populations, if its blood sodium level was significantly reduced during hibernation, would increase their infection to fungal and develop white-nose syndrome, causing widespread death of bats[41]. Such a finding may provide a physiological mechanism for an explanation of coexisting with various coronaviruses in bats and also indicate a possibility that many asymptomatic SARS-CoV-2 carriers may hold higher blood sodium levels and have lower expression of ACE2 in lower respiratory tract cells [Cryan, P. M. *et al*., 2013]. However, it could be recognized that the standardization and automatic detection methods for serum electrolytes used in modern hospitals could ensure the reliability of extracted data from the identified studies. In addition, for the retrospective cohort analysis, although a small cohort of 59 non-COVID-19 inpatients as control have provided very useful control data, however, it would be benefit to our conclusion if a normal control population matched with age and sex, etc., during the SARS-CoV-2 epidemic period. [Luo, Y . *et al*., 2020]

CONCLUSION

In conclusion, we found that people with low serum sodium (hyponatremia) may be related to susceptibility of SARS-CoV-2 infection and the development of severity of disease. This finding may provide an important idea to prevent the widespread prevalence of this virus or even other types of coronaviruses, and to treat the patients. In the epidemic stage, it may be of great significance to properly provide enough sodium intake or maintain blood sodium at a reasonable level for the susceptible population in order to reduce the virus infection and treat patients through therapeutic sodium supplementation (such as infusion) to prevent from the development of severe condition of disease. Cardiovascular symptoms (Bradycardia) associated with COVID-19 patients in our hospitalized could be potentially due to hyponatremia. Therefore, correction is important.

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