UMSHA Press

AJMB
Avicenna Journal of Medical Biochemistry

Avicenna J Med Biochem, 2023; 11(2):123-128. doi:10.34172/ajmb.2445

http://ajmb.umsha.ac.ir

Original Article

Investigating Hyponatremia Status and Interleukin 6 Concentration and Their Possible Relationship in COVID-19 Patients Compared to Healthy People

Fereshteh Mehri[1], Amirhossein Rahbar[2], Elaheh Talebi Ghane[3], Alireza Panahi[2], Maryam Esfahani[1*]

[1]Nutrition Health Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[2]Departments of Infectious Disease, Ayatollah Bahari Hospital, Hamadan University of Medical Sciences, Hamadan, Iran
[3]Modeling of Non-Communicable Diseases Search Center, Hamadan University of Medical Sciences Hamadan, Iran

Article history:
Received: June 18, 2023
Revised: July 27, 2023
Accepted: October 16, 2023
ePublished: November 20, 2023

***Corresponding author:**
Maryam Esfahani,
Email: esfahanimr21@yahoo.com

Abstract

Background: Systemic inflammation is associated with severe coronavirus disease. Hyponatremia can be caused by inflammation related to non-osmotic stimuli.

Objectives: This study was conducted to investigate hyponatremia status and interleukin 6 concentration as well as their possible relationship in COVID-19 patients compared to healthy people.

Methods: In this cross-sectional study, 24 COVID-19 patients and 24 healthy individuals referred to hospitals in Hamadan were included in the study in order to evaluate the relationship between hyponatremia and inflammation. The study was conducted after receiving ethical approval and informed consent from the participants. Complete blood count (CBC), inflammatory markers, electrolytes, creatinine, liver enzymes, ferritin, albumin, and D-dimer were measured using Selectra-Pro XI autoanalyzer, Pars Azmoun kits, and Human Interleukin 6 ELISA Kit Catalog MBS760693. All analyses were performed at a significance level of 0.05.

Results: In this study, there was no statistically significant difference in age and gender between 24 healthy people and 24 participating patients ($P>0.05$). The level of electrolytes such as sodium, potassium, magnesium, calcium, and phosphorus was significantly decreased in patients with COVID-19 compared to controls ($P<0.001$). The level of inflammatory markers, ferritin, albumin, D-dimer, and liver enzymes in the patient group was significantly increased compared to the control group ($P<0.01$).

Conclusion: The results of this study showed a higher incidence of hyponatremia and an increased level of interleukin-6 in COVID-19 patients. It seems that the use of strategies to reduce inflammation will help in the proper management of the disease.

Keywords: Hypernatremia, COVID-19, Inflammation, Electrolytes

Please cite this article as follows: Mehri F, Rahbar A, Talebi Ghane E, Panahi A, Esfahani M. Investigating hyponatremia status and interleukin 6 concentration and their possible relationship in COVID-19 patients compared to healthy people. Avicenna J Med Biochem. 2023; 11(2):123-128. doi:10.34172/ajmb.2445

Background

Hyponatremia (serum sodium concentration less than 135 mmol/L) is one of the most well-known electrolyte disorders of medical importance (1), which is associated with adverse clinical outcomes in patients with acute and chronic cardiopulmonary and pneumonia (2). Some studies on patients with community-acquired pneumonia (CAP) have reported the association of sodium disorders with increased mortality and an increased risk of admission to the intensive care unit considering that hyponatremia occurs in 26-28% of patients. The increase in the length of hospitalization is associated with an increase in hospital costs and an increase in the risk of mortality (3). Severe hyponatremia is associated with life-threatening complications, such as encephalopathy, cerebral edema, seizures, and coma. The risk of this disorder among pneumonia patients varies based on the type of pathogen. In other words, 44%-46% of Legionella pneumophila species cause hyponatremia, and 8%-14% of patients with CAP caused by other pathogens show hyponatremia (4). The severity of the underlying diseases is not a direct result of the cause of the disease, while in severe hyponatremia, this situation is the opposite. SARS-CoV-2 is a member of the coronavirus family and the cause of COVID-19 in 2019. In March 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic, which is one of the most severe pandemics that humanity has faced (5). Definitive evidence shows the relationship between

COVID-19 and the increase of inflammation; therefore, the occurrence of cytokine storm is one of the most important mechanisms of its pathogenesis (6). Some studies have shown the relationship between hyponatremia and the increase of inflammatory interleukins such as interleukin (IL)-6 and IL-1. Several results indicate the important role of IL-6 in the non-osmotic release of antidiuretic hormone (7). The plasma sodium level in pneumonia patients plays an important role in evaluating the severity of the disease and is used in assessing the severity of pneumonia (8). Numerous studies have shown electrolyte disturbances in COVID-19 patients, some of them show a decrease and other studies show an increase in sodium concentration in COVID-19 patients (6,9,10). Considering the importance of serum sodium and IL-6 levels in COVID-19 patients, the aim of this study was to investigate the status of serum sodium in these patients and its possible relationship with IL-6 compared to healthy control subjects in public hospitals in Hamedan, western Iran.

Materials and Methods

Study Design and Participants

This cross-sectional study was approved by the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1400.391). According to internal medicine specialists, the inclusion criteria for the patient and control groups were: having a definite positive real-time polymerase chain reaction (PCR) test result and CT-scan findings for COVID-19, not being intubated, and being at the age of 18 to 60 years. The exclusion criteria included: low glomerular filtration rate, suffering from various types of cancer, diabetes, hypertension, inflammatory diseases, or any disease that affects the level of interleukins (diagnosed by a specialist doctor), long-term use of drugs that suppress the immune system or drugs that affect the level of sodium (diagnosed by a specialist), pregnancy or breastfeeding, as well as smoking. In this way, 24 confirmed COVID-19 patients (confirmed by molecular PCR test and CT-scan findings) (men and women) and 24 healthy controls (men and women) referred to Ayatollah and Sinai hospitals in Hamadan were examined for periodical monitoring and chronic underlying diseases. In this study, in patient groups, 37 candidates were examined, of whom 8 individuals were excluded because they failed to meet the inclusion criteria and 6 volunteers withdrew from the study.

The patients were informed about the study, and the consent form was given to them in accordance with the research regulations of Hamadan University of Medical Sciences. The details of the admission of the patients were fully recorded, which included the demographic information of the patients, vital signs, fever, blood pressure, oxygen gas pressure, severity of the disease, hospitalization status in the ward, duration of hospitalization, and the outcome of the disease in all cases were recorded.

Sample Collection

After confirming COVID-19 by CT-scan findings and before prescribing any drug therapy, fasting blood samples were taken from patients and control subjects. After centrifuging the blood sample for 10 minutes at 3000 g, the serum was separated. Then, it was poured into 0.2 mL microtubes and kept in a freezer at -20 °C until the test.

Biochemical Tests

Common laboratory tests such as complete blood count (CBC) were performed using the Sysmex cell counter (SE 9020). Inflammatory markers such as *C-reactive protein* (CRP) (using the Bionic semi-quantitative latex agglutination kit) and erythrocyte sedimentation rate (ESR) (using the automatic ESR analyzer, Sedimex) were also measured. Electrolytes such as sodium, potassium, calcium, phosphorus, BUN, and creatinine, as well as liver enzymes including AST and ALT were measured using Selectra-Pro XI electrolyte analyzer and Pars Azmoun kits. Additionally, ferritin level was measured using Pishgaman kit Assay, and the albumin level was measured using the Man company kit. Besides, D-dimer level was measured with Pars Azmoun kit and Vaidas device, and IL-6 serum level was measured using the Human Interleukin 6 ELISA Kit Catalog MBS760693.

Statistical Analysis

In this study, frequency, percentages, mean and standard deviation are reported to describe the results. In order to compare the qualitative variables in two groups, chi-Square test was used, and independent *t*-test and Mann-Whitney U test were used to compare quantitative variables in two groups. All the tests were carried out at a significance level of 0.05 in SPSS version 26.0.

Results

A total of 24 healthy people and 24 COVID-19 patients participated in this study. The mean age of the participants in the healthy group was 42 ± 10.5 years and it was 48 ± 14.93 years in the patient group, indicating no significant difference ($P > 0.05$). In the control group, 75% were men and 25% were women, and in the patient group, 66.7% were men and 33.3% were women, indicating no significant difference between the two groups ($P > 0.05$). All participants were comparable in terms of age and gender. The main characteristics of the respondents are shown in Table 1. There was no underlying disease in any of the participants. The control group did not receive drugs, but those with COVID-19 received favipiravir, vitamin C, vitamin D, acetaminophen, diphenhydramine syrup, and Seroflo spray. Moreover, 81% of the patients had moderate disease and 19% had a severe condition and were admitted to the intensive care unit. Fortunately, only two deaths occurred in the patient group (9.5%). Additionally, 88.9% of patients had a CT scan. Table 1 shows demographic information and clinical characteristics of the participants. In this study, the levels of other electrolytes such as

Table 1. Demographic and Clinical Characteristics of COVID-19 Patients and Healthy Controls

Property	Patient Group	Control Group	*P* Value
Number of people	24	24	
Gender (male) (%)	66.7%	75%	0.538
Body temperature (°C)	0.5 ± 39.1	0.1 ± 37	0.03
Cough	66.7%	-	-
Systolic pressure (mm Hg)	0.5 ± 120.7	0.6 ± 120.1	0.723
Diastolic pressure (mm Hg)	0.5 ± 7.3	0.8 ± .7.8	0.685
Oxygen saturation percentage	5.2 ± 87	1 ± 97	-
Respiratory distress	58%	-	-
Muscular pain	71.4%	-	-
Stomachache	23.3%	-	-
Nausea	28.6%	-	-
Vomiting	33.3%	-	-
Diarrhea	23.8%	-	-
Anorexia	57.1%	-	-
Headache	66.7%	-	-
Dizziness	14.3%	-	-
Marked CT scan	88.19%	-	-
Hospitalization period (days)	10.38%	-	-
General admission department	76.2%	-	-
Hospitalization in the intensive care unit	90%	-	-
Clinical outcome of the disease (discharge)	10%	-	-

potassium, magnesium, calcium, and phosphorus were also measured. Based on the results, the serum level of sodium in COVID-19 patients showed a significant decrease compared to the control group ($P < 0.001$). There was also a significant decrease in the concentration of other electrolytes such as magnesium and potassium ($P < 0.001$). Phosphorus and calcium levels were also decreased in the patient group. A decrease in albumin concentration was also observed in the patient group. The measurement of inflammatory markers such as ESR, CRP, IL-6, and ferritin in both groups showed a significant increase in the serum level of these inflammatory markers in the patient group compared to the control group ($P < 0.001$). The increase in the level of D-dimer and CPK and LDH enzymes was also significant in COVID-19 patients. Biochemical analyses were also performed in two groups, the results of which are presented in Table 2. The changes in non-fasting blood sugar, BUN, and creatinine levels in the patient group were significantly increased compared to the control group ($P < 0.01$). The increase of liver enzymes in the patient group was also significant compared to the control group ($P < 0.01$). In the patient group, serum levels of IL-6 and sodium showed a negative significant relationship with a correlation coefficient of 0.81 ($P < 0.001$). It should be noted that no significant relationship was observed between IL-6 serum level and D-dimer with a correlation coefficient of 0.047 ($P < 0.858$) Table 3.

Table 2. The Serum Levels of Biochemical Parameters in COVID-19 Patients and Healthy Controls

Biochemical Analytes	Patient group Mean (SD)	Control group Mean (SD)	*P* Value
Sodium (mEq/L)	128.7 ± 10	142.2 ± 7	< 0.001
Potassium (mEq/L)	4 ± 0.6	4.5 ± 0.8	< 0.001
Blood sugar (mg/dL)	141.8 ± 24.8	92.5 ± 2.17	0.099
BUN (mg/dL)	22.9 ± 4.7	14.5 ± 1.3	0.001
Creatinine (mg/dL)	1.1 ± 0.2	0.8 ± 0.1	0.001
Aspartate aminotransferase (U/L)	49.6 ± 7.4	18. ± 6.2	< 0.001
Alanine aminotransferase (U/L)	23.3 ± 6.7	22.2 ± 7.8	0.011
Alkaline phosphatase (IU/L)	177.2 ± 31	159.4 ± 16.5	0.246
Calcium (mg/dL)	7.6 ± 0.4	9.3 ± 0.6	0.031
Magnesium (mg/dL)	1.9 ± 0.2	0.2 ± 1.2	0.001
Phosphorus (mg/dL)	3.5 ± 0.4	4.5 ± 0.5	< 0.001
Creatine phosphokinase (mcg/L)	261.4 ± 34.4	14.9 ± 19.6	0.006
Lactate dehydrogenase (IU/L)	425.5 ± 34.9	171.5 ± 40.8	< 0.001
Albumin (g/dL)	3.8 ± 0.2	4.3 ± 0.4	0. 01
D-dimer (ng/mL)	1225 ± 98.8	187.7 ± 29.4	< 0.001

Table 3. The Serum Levels of Inflammatory Indicators in the COVID-19 Patients and Healthy Controls

Biomarkers	Patient	Control	*P* Value
IL-6 level (pg/mL)	3.39 ± 0.9	0.55 ± 0.13	< 0.001
CRP	3.44 ± 1.1	7.24 ± 54.7	< 0.001
ESR	16.7 ± 2.5	49.8 ± 19.2	< 0.01
Ferritin (mcg/L)	342 ± 61.6	16.4 ± 56.7	< 0.001
The percentage of lymphocytes	22%	39%	< 0.01
Absolute lymphocyte count (/μL)	1423 ± 281.3	2813 ± 178.4	< 0.01

IL-6: Interleukine-6; CRP: C-Reactive protein; ESR: Estimated sedimentation rate.

Discussion

More than 150 million people have been infected with SARS-CoV-2, and the pandemic caused by this virus has become the world's biggest health concern. The virus enters the host cells through angiotensin-converting enzyme 2 receptors (11). These receptors are expressed in many organs and are responsible for many physiological processes such as regulation of renin angiotensin system, blood pressure, and electrolyte balance (12). The COVID-19 virus can activate various molecular pathways that cause the complexity of pathogenesis and its clinical results, including the death of type 1 pneumocytes, interference with the renin-angiotensin system, disruption of iron metabolism, activation of intravascular coagulation, which can lead to death. As mentioned before, the ACE2 receptor, the main entry point into the human cells for SARS-CoV-2, is a zinc carboxypeptidase, which is associated with the ability of the virus to disrupt iron homeostasis and increase serum ferritin level. This study has caused researchers to trace elements involved in the clinical course of COVID-19 (13). Lung diseases are among the most important causes of hyponatremia, which

occurs in more than 30% of people with pneumonia. Various studies have shown the relationship between serum sodium concentration (hypo and hypernatremia) and mortality in hospitalized patients and introduced it as an independent risk factor for mortality (11). In this study, more than 90% of patients had hyponatremia. This finding is consistent with previous reports showing that hyponatremia is more common than hypernatremia in patients with CAP who have sodium disorder (13). Meta-analysis studies with 37% sensitivity and 82% specificity have associated hyponatremia with adverse clinical outcomes of COVID-19, such as mortality, prolonged hospitalization, and severity of COVID-19 (such as severe pneumonia or requiring intensive care unit or invasive mechanical ventilation). In the condition of normal sodium level, there is a 16% probability of a bad prognosis of COVID-19, and in the presence of hyponatremia, this probability increases to 33% (14). Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been proposed as one of the important causes of hyponatremia, and factors such as pain, nausea, and some drugs trigger this condition (15). Another factor contributing to the occurrence of SIADH in pneumonia is hypoxic pulmonary vasoconstriction followed by the reduction of left ventricular filling, which leads to the increase of ADH secretion (16). Inflammation and increased IL-6 levels are factors involved in the non-osmotic release of ADH (16). The results of this study showed that the level of IL-6 in COVID-19 patients had a significant increase compared to control subjects. Retrospective studies also show that 22.9% of COVID-19 patients had hyponatremia during admission, which was associated with adverse respiratory function and increased IL-6 levels in these patients compared to normothermic patients (17). Research has proven that hyponatremia is related to various inflammatory diseases such as pneumonia, acute respiratory distress syndrome, tuberculosis, and meningitis (18). Studies show that inflammatory cytokines such as IL-1β and IL-6 are involved in the development of hyponatremia associated with inflammatory conditions (19). Laboratory studies have proven that inflammatory interleukins such as IL-1B can cause central and peripheral release of vasopressin and IL-6 can induce ADH secretion in two ways: direct stimulation of the hypothalamus and damage to the alveolar basement membrane and lung (20). Additionally, studies have shown that IL-6 causes early activation of arginine vasopressin neurons in response to the injection of bacterial lipopolysaccharide (21). More importantly, Palin et al proved that 2 hours after the injection of IL-6, the level of arginine vasopressin increases (21). These researchers suggest that inflammatory interleukin causes the activation of vasopressin-secreting neurons and there is a possibility that they cause SIADH (20). Our previous study proved the existence of oxidative stress in COVID-19 patients (22). ROS stimulates the breakdown of lipid membranes and changes the redox status of proteins involved in osmotransduction, especially osmotically activated tyrosine kinases (such as ERK1/2, p38, members of the src family), these changes increase their activity and change cellular homeostasis (23). In this study, D-dimer level was significantly increased in COVID-19 patients. The D-dimer level has been proposed as a biomarker for the severity and mortality of COVID-19 (24). The results of the study by Zhang et al on COVID-19 patients showed that D-dimer level is a useful early marker in the control and management of this disease (25). Among other findings of this study, there was a significant relationship between sodium level and serum D-dimer level ($P < 0.05$) and IL-6 level ($P < 0.05$). A high D-dimer level not only indicates a hypercoagulable state but also confirms the presence of inflammation (26). The existence of a relationship between electrolyte disorders, especially hyponatremia, and D-dimer levels has been studied in other diseases. Accordingly, the sodium/D-dimer ratio has recently been proposed as a factor predicting the effect of first-line chemotherapy as well as a prognostic factor in patients with advanced gastric cancer (27). Although it seems that the common point of hyponatremia and the increase of D-dimer level is the presence of inflammatory conditions, the exact mechanism is not clear and more investigation is definitely needed. The results of this study showed that COVID-19 affects the level of other electrolytes. In other words, a decrease in the serum concentration of potassium, magnesium, phosphorus, and calcium was observed. In a study conducted by Liu et al in 2020, electrolyte disorders were observed in hospitalized patients with COVID-19, including hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia, and hypoalbuminemia. Hypocalcemia has been attributed to the hypoalbuminemia present in COVID-19 patients (28). Albumin has different bioactive roles and in addition to its antioxidant function, it affects the concentration of electrolytes. Hypoalbuminemia causes a shift of fluid from the plasma to interstitial spaces, decrease in serum volume, release of ADH, and hyponatremia. A decrease in albumin concentration has been reported in COVID-19 patients (27). As mentioned before, in this study, there was a decrease in serum magnesium concentration in the patient group compared to the control group. It has been hypothesized that reducing the concentration of magnesium can change the clinical condition of COVID-19 from mild to severe. Magnesium has a regulatory effect on the cytotoxic functions of natural killer cells (NK) and CD8 + T lymphocytes (29). The reduction of NK and T-cell cytotoxicity due to magnesium deficiency can indicate the greater susceptibility of the elderly and people with high blood pressure, obesity, and diabetes to COVID-19. Besides, magnesium deficiency increases the production of inflammatory cytokines in monocytes and increases the expression of NF-κβ; therefore, hypomagnesemia has pro-inflammatory activity (30). Considering the occurrence of cytokine storm in COVID-19 and the fact that ATP reproduction after cytokine storm requires sufficient level

of magnesium, it can be concluded that hypomagnesemia can aggravate the condition of the disease. In this study, hypokalemia was also observed in the patient group. Various mechanisms, such as the increase in the activity of the renin-angiotensin system (resistance of the virus to this system), damage of digestive system, anorexia secondary to the disease, and tubular damage caused by ischemia or nephrotoxic factors are involved in the occurrence of hypokalemia in COVID-19. Tubular damage can be caused by the direct cytotoxic effect of the virus (31). The results of a study by Alfano et al showed that hypokalemia occurred in half of the COVID-19 patients within the first 24 hours of hospitalization. The incidence of hypokalemia was associated with a significant prolongation of hospitalization (32). In severe cases, hypokalemia is associated with life-threatening complications such as arrhythmic heart disorders, paralysis, and rhabdomyolysis, especially in people with cardiovascular diseases. Another important point is that due to the association of hypokalemia with QT prolongation, serum potassium should be carefully measured in these patients because some drugs used in COVID-19, such as azithromycin and hydroxychloroquine, also affect QT. This study had limitations, including the small size of the selected sample, as well as the impossibility of measuring the excretion of sodium and other electrolytes, especially in the urine sample. Moreover, if it is possible to measure the serum level of ADH, it would be possible to determine the type of hyponatremia more accurately.

Conclusion

Hyponatremia is one of the most common electrolyte disorders in COVID-19 patients. Our study showed a higher incidence of hyponatremia and an increased level of interleukin-6 in COVID-19 patients, indicating a significant relationship between these two. Determining the etiology of this disorder is very important in these patients because it can determine the type of treatment. In this study, the reduction of other electrolytes such as hypomagnesemia, hypokalemia, and hypocalcemia was also observed. More studies are needed to accurately determine the pathogenesis of these disorders.

Acknowledgments

This study was derived from a research project conducted at Hamadan University of Medical Sciences (project number: 140007276144). The authors would like to thank the Research and Technology Vice-Chancellor for providing support and assistance in implementing the project.

Authors' Contribution

Conceptualization: Amirhossein Rahbar.
Data curation: Alireza Panahi.
Formal analysis: Elaheh Talebi Ghane.
Funding acquisition: Maryam Esfahani.
Investigation: Fereshteh Mehri.
Methodology: Fereshteh Mehri.
Project administration: Maryam Esfahani.
Resources: Amirhossein Rahbar.
Software: Elaheh Talebi Ghane.
Supervision: Fereshteh Mehri.
Validation: Fereshteh Mehri.
Visualization: Maryam Esfahani.
Writing–original draft: Fereshteh Mehri.
Writing–review & editing: Fereshteh Mehri.

Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

The present study was derived from a research project conducted at Hamadan University of Medical Sciences and was approved by the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1400.391).

Funding

This project was supported by Hamadan University of Medical Sciences.

References

1. Singhi S. Hyponatremia in hospitalized critically ill children: current concepts. Indian J Pediatr. 2004;71(9):803-7. doi: 10.1007/bf02730718.
2. Scherz N, Labarère J, Méan M, Ibrahim SA, Fine MJ, Aujesky D. Prognostic importance of hyponatremia in patients with acute pulmonary embolism. Am J Respir Crit Care Med. 2010;182(9):1178-83. doi: 10.1164/rccm.201003-0481OC.
3. Nair V, Niederman MS, Masani N, Fishbane S. Hyponatremia in community-acquired pneumonia. Am J Nephrol. 2007;27(2):184-90. doi: 10.1159/000100866.
4. Fiumefreddo R, Zaborsky R, Haeuptle J, Christ-Crain M, Trampuz A, Steffen I, et al. Clinical predictors for *Legionella* in patients presenting with community-acquired pneumonia to the emergency department. BMC Pulm Med. 2009;9:4. doi: 10.1186/1471-2466-9-4.
5. Gheorghe G, Ilie M, Bungau S, Stoian AMP, Bacalbasa N, Diaconu CC. Is there a relationship between COVID-19 and hyponatremia? Medicina (Kaunas). 2021;57(1):55. doi: 10.3390/medicina57010055.
6. Picchianti Diamanti A, Rosado MM, Pioli C, Sesti G, Laganà B. Cytokine release syndrome in COVID-19 patients, a new scenario for an old concern: the fragile balance between infections and autoimmunity. Int J Mol Sci. 2020;21(9):3330. doi: 10.3390/ijms21093330.
7. Gionis D, Ilias I, Moustaki M, Mantzos E, Papadatos I, Koutras DA, et al. Hypothalamic-pituitary-adrenal axis and interleukin-6 activity in children with head trauma and syndrome of inappropriate secretion of antidiuretic hormone. J Pediatr Endocrinol Metab. 2003;16(1):49-54. doi: 10.1515/jpem.2003.16.1.49.
8. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336(4):243-50. doi: 10.1056/nejm199701233360402.
9. Pourfridoni M, Abbasnia SM, Shafaei F, Razaviyan J, Heidari-Soureshjani R. Fluid and electrolyte disturbances in COVID-19 and their complications. Biomed Res Int. 2021;2021:6667047. doi: 10.1155/2021/6667047.
10. De Carvalho H, Richard MC, Chouihed T, Goffinet N, Le Bastard Q, Freund Y, et al. Electrolyte imbalance in COVID-19 patients admitted to the emergency department: a case-control study. Intern Emerg Med. 2021;16(7):1945-50. doi: 10.1007/s11739-021-02632-z.
11. Sever P, Johnston SL. The renin-angiotensin system and SARS-CoV-2 infection: a role for the ACE2 receptor? J Renin Angiotensin Aldosterone Syst. 2020;21(2):1470320320926911. doi: 10.1177/1470320320926911.

12. Nehme A, Zouein FA, Zayeri ZD, Zibara K. An update on the tissue renin angiotensin system and its role in physiology and pathology. J Cardiovasc Dev Dis. 2019;6(2):14. doi: 10.3390/jcdd6020014.
13. Faa G, Saba L, Fanni D, Kalcev G, Carta M. Association between hypomagnesemia, COVID-19, respiratory tract and lung disease. Open Respir Med J. 2021;15:43-5. doi: 10.2174/1874306402115010043.
14. Akbar MR, Pranata R, Wibowo A, Irvan, Sihite TA, Martha JW. The prognostic value of hyponatremia for predicting poor outcome in patients with COVID-19: a systematic review and meta-analysis. Front Med (Lausanne). 2021;8:666949. doi: 10.3389/fmed.2021.666949.
15. Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med. 2007;356(20):2064-72. doi: 10.1056/NEJMcp066837.
16. Koizumi K, Yamashita H. Influence of atrial stretch receptors on hypothalamic neurosecretory neurones. J Physiol. 1978;285:341-58. doi: 10.1113/jphysiol.1978.sp012575.
17. Berni A, Malandrino D, Corona G, Maggi M, Parenti G, Fibbi B, et al. Serum sodium alterations in SARS CoV-2 (COVID-19) infection: impact on patient outcome. Eur J Endocrinol. 2021;185(1):137-44. doi: 10.1530/eje-20-1447.
18. Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol. 2011;118(2):45-51. doi: 10.1159/000322238.
19. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr. 2013;56(12):519-22. doi: 10.3345/kjp.2013.56.12.519.
20. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-8. doi: 10.1093/cid/ciaa248.
21. Palin K, Moreau ML, Sauvant J, Orcel H, Nadjar A, Duvoid-Guillou A, et al. Interleukin-6 activates arginine vasopressin neurons in the supraoptic nucleus during immune challenge in rats. Am J Physiol Endocrinol Metab. 2009;296(6):E1289-99. doi: 10.1152/ajpendo.90489.2008.
22. Mehri F, Rahbar AH, Talebi Ghane E, Souri B, Esfahani M. Changes in oxidative markers in COVID-19 patients. Arch Med Res. 2021;52(8):843-9. doi: 10.1016/j.arcmed.2021.06.004.
23. Fibbi B, Marroncini G, Anceschi C, Naldi L, Peri A. Hyponatremia and oxidative stress. Antioxidants (Basel). 2021;10(11):1768. doi: 10.3390/antiox10111768.
24. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol. 2020;13(11):1265-75. doi:10.1080/17474086.2020.1831383.
25. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with COVID-19. J Thromb Haemost. 2020;18(6):1324-9. doi: 10.1111/jth.14859.
26. Davalos D, Akassoglou K. Fibrinogen as a key regulator of inflammation in disease. Semin Immunopathol. 2012;34(1):43-62. doi: 10.1007/s00281-011-0290-8.
27. Chen C, Zhang Y, Zhao X, Tao M, Yan W, Fu Y. Hypoalbuminemia - an indicator of the severity and prognosis of COVID-19 patients: a multicentre retrospective analysis. Infect Drug Resist. 2021;14:3699-710. doi: 10.2147/idr.s327090.
28. Liu D, Fisher M, Basalely AM, Kumar ND, Thakkar J, Golestaneh L, et al. Electrolyte abnormalities in hospitalized patients with COVID-19. J Am Soc Nephrol. 2020;31:306.
29. Chaigne-Delalande B, Li FY, O'Connor GM, Lukacs MJ, Jiang P, Zheng L, et al. Mg2 + regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. Science. 2013;341(6142):186-91. doi: 10.1126/science.1240094.
30. Weglicki WB. Hypomagnesemia and inflammation: clinical and basic aspects. Annu Rev Nutr. 2012;32:55-71. doi: 10.1146/annurev-nutr-071811-150656.
31. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219-27. doi: 10.1016/j.kint.2020.04.003.
32. Alfano G, Ferrari A, Fontana F, Perrone R, Mori G, Ascione E, et al. Hypokalemia in patients with COVID-19. Clin Exp Nephrol. 2021;25(4):401-9. doi: 10.1007/s10157-020-01996-4.