# ELECTROLYTE DISORDERS IN COVID PATIENTS

DR.M.Amerian

- The novel coronavirus disease 2019 (COVID-19) is the cause of an acute respiratory illness which has spread around the world.

- The virus infects the host by binding to the angiotensin-converting enzyme 2 (ACE2) receptors. Due to the presence of ACE2 receptors in the kidneys and gastrointestinal (GI) tract, kidneys and GI tract damage arising from the virus can be seen in patients and can cause acute conditions such as acute kidney injury (AKI) and digestive problems for the patient.

- One of the complications of kidneys and GI involvement in COVID-19 is fluid and electrolyte disturbances. The most common ones of these disorders are hyponatremia, hypernatremia, hypokalemia, hypocalcemia, hypochloremia, hypervolemia, and hypovolemia, which if left untreated, cause many problems for patients and even increase mortality.
- Fluid and electrolyte disturbances are more common in hospitalized and intensive care patients.

- Dysnatremia is associated with increased mortality in patients with community-acquired pneumonia. SARS-COV2 (Severe-acute-respiratory syndrome caused by Coronavirus-type 2) pneumonia can be fatal.

- The presence of tachypnea was independently associated with both hyponatremia and hypernatremia, although the mechanisms are not clear. Tachypnea increases insensible body fluid loss. Additionally, the reduction in oral intake secondary to the hyporexia or anorexia described in some patients with COVID-19 (26) could be directly worsened by tachypnea itself, since a higher respiratory rate makes solid food and fluid intake more difficult.

- Hyponatremia is the most common electrolyte abnormality in patients with bacterial pneumonia, is usually attributed to the syndrome of inappropriate antidiuresis (SIADH) or hypervolemia, and predicts poor outcome.

- Infection can cause excess release of pro-inflammatory Accepted Manuscript 6 cytokines, such as interleukin-1β (IL-1β) and interleukin-6 (IL-6), which induce nonosmotic release of arginine vasopressin (AVP), causing hyponatremia due to SIADH . Therefore, hyponatremia is a good surrogate marker of the degree of inflammatory response, reflecting the severity of various infections

- It is known that hyponatremia, even when mild, is associated with a worse outcome and an increased risk of death in different pathological conditions, including pneumonia , heart failure , acute myocardial infarction , cirrhosis , cancer , elderly patients , and intensive care patients . These data have been confirmed by an extensive meta-analysis, which included 82 publications for a total of more than 850 000 patients

- . A relative or absolute excess of fluid versus solute intake (the latter found primarily in solids) could favor the development of hyponatremia. Where fluid intake was extremely low, and solute intake relatively conserved, dehydration and hypernatremia could ensue.
- Some drugs previously used in the United States Food and Drug Administration's (FDA) treatment protocol for patients with COVID19, such as chloroquine and hydroxychloroquine, can cause electrolyte imbalance.

frontiers in Endocrinology

ORIGINAL RESEARCH
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# Prognostic Impact of Hyponatremia and Hypernatremia in COVID-19 Pneumonia. A HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19) Registry Analysis

*Jorge Gabriel Ruiz-Sánchez[1]*, Ivan J. Núñez-Gil[1], Martin Cuesta[1,2], Miguel A. Rubio[1], Charbel Maroun-Eid[3], Ramón Arroyo-Espliguero[4], Rodolfo Romero[5], Victor Manuel Becerra-Muñoz[6], Aitor Uribarri[7], Gisela Feltes[8], Daniela Trabattoni[9], María Molina[10], Marcos García Aguado[11], Martino Pepe[12], Enrico Cerrato[13], Emilio Alfonso[14], Alex Fernando Castro Mejía[15], Sergio Raposeiras Roubin[16], Luis Buzón[17], Elvira Bondia[18], Francisco Marin[19], Javier López Pais[20], Mohammad Abumayyaleh[21], Fabrizio D'Ascenzo[22], Elisa Rondano[23], Jia Huang[24], Cristina Fernandez-Perez[1], Carlos Macaya[1], Paz de Miguel Novoa[1], Alfonso L. Calle-Pascual[1,2], Vicente Estrada Perez[1], Isabelle Runkle[1] and HOPE COVID-19 investigators[1]*

[1] Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain, [2] Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain, [3] Hospital Universitario La Paz, Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Madrid, Spain, [4] Hospital Universitario Guadalajara, Guadalajara, Spain, [5] Hospital Universitario Getafe, Universidad Europea de Madrid, Madrid, Spain, [6] Hospital Clinico Universitario Virgen de la Victoria, Málaga, Spain, [7] Hospital Clinico Universitario de Valladolid, Valladolid, Spain, [8] Hospital Nuestra Señora de América, Madrid, Spain, [9] Centro Cardiologico Monzino, IRCCS,

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**Edited by:**
*Giovanna Mantovani, University of Milan, Italy*

**Reviewed by:**
*Alessandro Peri, University of Florence, Italy*
*Mirjam Christ-Crain, University Hospital of Basel, Switzerland*

***Correspondence:**
*Jorge Gabriel Ruiz-Sánchez*
*gajo_saru@hotmail.com*

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- . In this multicentric study of 4,664 patients hospitalized with COVID19, we found that admittance hyponatremia was frequent, affecting more than 20% of patients, for a total of 9
- 57 subjects. Conversely, hypernatremia was found in only 3.7%, a total of 174 subjects.
- In the current study, multivariable analysis indicated that CKD and bilateral pneumonia, as well as tachypnea, male sex, and an age ≥70 years, were linked to decreased SNa levels or the presence of hyponatremia. We found a higher rate of therapy with ACEi/ARBs in hyponatremic patients as compared with eunatremic subjects, but these treatment regimens were not independently associated with either a low SNa or the presence of hyponatremia .

- . Furthermore, smoking, tachypnea, and a SC ≥1.5 mg/dl were independently associated with the presence of admission hypernatremia.

- . Our study also detected a J-shaped curve when plotting mortality risk against SNa, indicating that risk of mortality  progressively increases as SNa descends below 137 mmol/L (Figure 2), until reaching a SNa of 120 mmol/L.

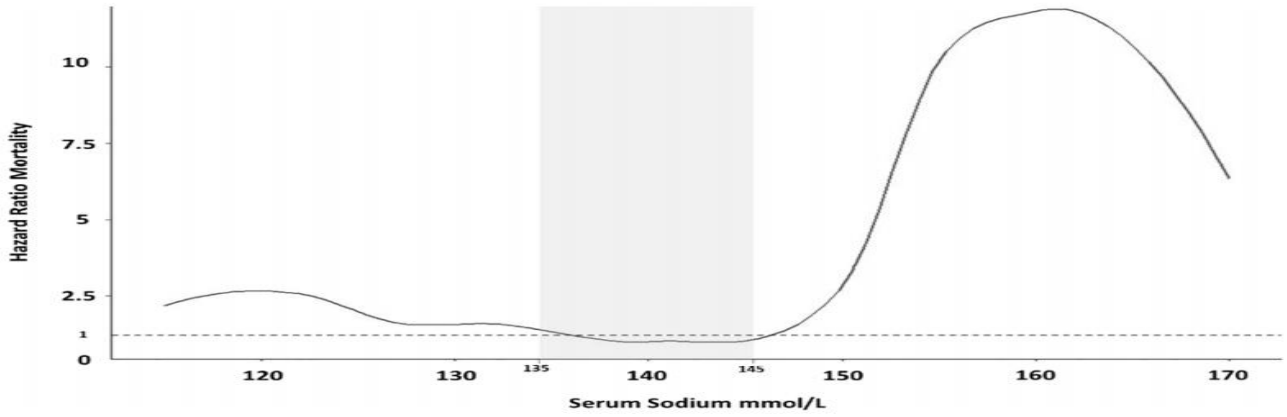


**FIGURE 2** | Hazzard Ratios for mortality according to serum sodium in the entire group of patients. Developed with a Univariate Cox regression analysis.

- Hypernatremia at any timepoint during hospital stay is related to excess in-hospital mortality, while hyponatremia at presentation is associated with a higher likelihood to require advanced ventilatory support. Hyponatremia was not a risk factor for in hospital mortality, except for the subgroup of hypovolemic hyponatremia.

- Therefore, serum sodium values could be used in clinical practice to identify patients with COVID-19 at high risk of poor outcomes who would benefit from more intensive monitoring and judicious rehydration

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Research Paper

# Association Between Average Plasma Potassium Levels and 30-day Mortality During Hospitalization in Patients with COVID-19 in Wuhan, China

Shengcong Liu, M.D.[1,2], Long Zhang, M.D.[1,2], Haoyu Weng, M.D.[1,2], Fan Yang, M.D.[1,2], Han Jin, M.D.[1,2], Fangfang Fan, M.D.[1,2], Xizi Zheng, M.D.[3], Hongyu Yang, M.D.[3], Haichao Li, M.D.[4], Yan Zhang, M.D.[1,2,5]✉, Jianping Li, M.D.[1,2,5]✉

1. Department of Cardiology, Peking University First Hospital, Beijing, China
2. Institute of Cardiovascular Disease, Peking University First Hospital, Beijing, China
3. Department of Nephrology, Peking University First Hospital, Beijing, China
4. Department of Respiratory and Critical Care Medicine, Peking University First Hospital, Beijing, China
5. Key Laboratory of Molecular Cardiology Sciences of the Ministry of Education, Peking University Health Science Center, Beijing, China

✉ Corresponding author: Yan Zhang, M.D., Department of Cardiology, Peking University First Hospital, Beijing, China, No. 8 Xishiku Street, Xicheng District, Beijing, China. E-mail: 07677@pkufh.com; drzhy1108@163.com; Tel: 8610-83575260; Fax: 8610-66137748

## Abstract

**Background:** Coronavirus disease 2019 (COVID-19) has resulted in more than 610,000 deaths worldwide since December 2019. Given the rapid deterioration of patients' condition before death, markers with efficient prognostic values are urgently required. During the treatment process, notable changes in plasma potassium levels have been observed among severely ill patients. We aimed to evaluate the association between average plasma potassium ($K_a^+$) levels during hospitalization and 30-day mortality in patients with COVID-19.

**Methods:** Consecutive patients with COVID-19 hospitalized in the Zhongfaxincheng branch of Tongji Hospital in Wuhan, China from February 8 to 28, 2020 were enrolled in this study. We followed patients up to 30 days after admission.

**Results:** A total of 136 patients were included in the study. The average age was 62.1±14.6 years and 51.5% of patients were male. The median baseline potassium level was 4.3 (3.9–4.6) mmol/L and $K_a^+$ level during hospitalization was 4.4 (4.2–4.7) mmol/L; the median number of times that we measured potassium was 4 (3–5). The 30-day mortality was 19.1%. A J-shaped association was observed between $K_a^+$ and 30-day mortality. Multivariate Cox regression showed that compared with the reference group ($K_a^+$ 4.0 to <4.5 mmol/L), 30-day mortality was 1.99 (95% confidence interval [CI]=0.54–7.35, P=0.300), 1.14 (95% CI=0.39–3.32, P=0.810), and 4.14 (95% CI=1.29–13.29, P=0.017) times higher in patients with COVID-19 who had $K_a^+$ <4.0, 4.5 to <5.0, and ≥5.0 mmol/L, respectively.

**Conclusion:** Patients with COVID-19 who had a $K_a^+$ level ≥5.0 mmol/L had a significantly increased 30-day mortality compared with those who had a $K_a^+$ level 4.0 to <4.5 mmol/L. Plasma potassium levels should be monitored routinely and maintained within appropriate ranges in patients with COVID-19.

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Case Report

# Persistent Hypokalemia post SARS-coV-2 infection, is it a life-long complication? Case report

Mohammed Obaid Alnafiey [a,*,1], Abdullah Meshari Alangari [a,1], Abdullah Mohammed Alarifi [b], Ahmed Abushara [c,2]

[a] *Department of Internal Medicine, KSMC, Alimam Turki Ibn Abdullah Ibn Muhammed, Ulaishah, Riyadh, 12746, Saudi Arabia*
[b] *Saudi Electronic University, P.O.Box: 32109, Riyadh, 11428, Saudi Arabia*
[c] *Department of Hematology and Oncology, KSMC, Alimam Turki Ibn Abdullah Ibn Muhammed, Ulaishah, Riyadh, 12746, Saudi Arabia*

A B S T R A C T

*Introduction and importance:* SARS-CoV-2 is a novel infection that has affected millions of people around the world. Complications of the infection may affect multiple systems including cardiovascular, neurological, gastrointestinal, urinary, and pulmonary systems. Hypokalemia, which is a life-threatening condition that may lead to arrhythmia and possibly death, has been noticed in more than half of the COVID-19 patients. Further understanding of the disease process and its complications is necessary to guide in preventing the complications from happening in the first place and finding treatment for patients with an already established complications.
*Case presentation:* A 34-year old male from Philippines who lives in Saudi Arabia – Riyadh and works as health care provider with no previous history of any medical illness. Presented by himself to the emergency department (ED) with dry cough, shortness of breath, fever, malaise, and fatigability for five days. On examination (RR 25), (T 38.6 °C) and (O2 89% Room air), on auscultation there was a decrease on air entry bilaterally with scattered crepitations, no wheezing or stridor. Covid-19 swab was positive, (Day 1) potassium 2.91 (mmol/L) magnesium (mmol/L) with normal baseline before getting infected.
*Clinical discussion:* Patient while in the hospital was on daily potassium oral and IV replacement with IV magnesium replacement. Investigation showed 24Hr urine potassium 47.3 (mmol/L), 24Hr urine magnesium 5.52 (mmol/L), 24Hr urine Creatinine 9.25 (mmol/L), (TTKG) Transtubular Potassium Gradient 18 and (VBG) PH:7.38, Pco2:44 (mmHg) Po2:55 (mmHg) HCO3:25 (mEq/L). Patient has an increased renal potassium loss with normal VBG on separate days and normal Blood pressure that excludes diseases with associated acidemia or alkalemia. Our patient didn't want to go for any invasive diagnostic procedures and favored to wait for spontaneous recovery.
*Conclusion:* We followed up the potassium level of our patient for more than 5 months since he was diagnosed with COVID-19 to find out that he is still having hypokalemia, as well as, hypomagnesemia. Long term complications of COVID-19 infection such as hypokalemia and hypomagnesemia need to be observed and followed up closely to avoid life-threatening arrythmias and seizures. The attention of the scientific community to possible long term or permanent complications is needed to help find preventive measures and treatment for patients with complications.

- In a healthy person, RAS activity is balanced by ACE1 (which increases RAS activity) and ACE2 (which decreases RAS activity) [22]. When SARS-CoV-2 binds and degrades ACE2, the ability of ACE2 to regulate RAS is reduced and it cannot antagonize ACEI-2. The final result is RAS activity is increased, which acts like secondary increased aldosterone [17]. Increased RAS activity enhances the distal delivery of sodium and water to collecting tubule of the kidney and the excretion of potassium, because previous literature also has shown that serum K+ is negatively associated with plasma renin activity [23].

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# Hypokalemia as a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia: A case series of 306 Mediterranean patients

Oscar Moreno-Pérez[a,b,*], Jose-Manuel Leon-Ramirez[c], Laura Fuertes-Kenneally[d], Miguel Perdiguero[e], Mariano Andres[b,f], Mar Garcia-Navarro[g], Paloma Ruiz-Torregrosa[c], Vicente Boix[b,h], Joan Gil[c], Esperanza Merino[h], On behalf of COVID19-ALC Research Group

[a] *Endocrinology and Nutrition Department, Alicante General University Hospital – Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain*
[b] *Clinical Medicine Department, Miguel Hernández University, Elche, Spain*
[c] *Pneumology Department, Alicante General University Hospital – Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain*
[d] *Cardiology Department, Alicante General University Hospital – Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain*
[e] *Nephrology Department, Alicante General University Hospital – Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain*
[f] *Rheumatology Department, Alicante General University Hospital – Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain*
[g] *Internal Medicine Department, Alicante General University Hospital – Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain*
[h] *Unit of Infectious Diseases, Alicante General University Hospital – Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain*

A B S T R A C T

*Objectives:* Serum levels of potassium ($K^+$) appear to be significantly lower in severe cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the clinical significance of this is unknown. The objective was to investigate whether hypokalemia acts as a biomarker of severity in coronavirus disease 2019 (COVID-19) pneumonia and is associated with major clinical outcomes.
*Methods:* A retrospective cohort study of inpatients with COVID-19 pneumonia (March 3 to May 2, 2020) was performed. Patients were categorized according to nadir levels of $K^+$ in the first 72 h of admission: hypokalemia ($K^+ \leq 3.5$ mmol/l) and normokalemia ($K^+ > 3.5$ mmol/l). The main outcomes were all-cause mortality and the need for invasive mechanical ventilation (IMV); these were analyzed by multiple logistic regression (odds ratio (OR), 95% confidence interval (CI)).
*Results:* Three hundred and six patients were enrolled. Ninety-four patients (30.7%) had hypokalemia and these patients showed significantly higher comorbidity (Charlson comorbidity index $\geq 3$, 30.0% vs 16.3%; $p = 0.02$) and CURB65 scores (median (interquartile range): 1.5 (0.0–3.0) vs 1.0 (0.0–2.0); $p = 0.04$), as well as higher levels of some inflammatory parameters at baseline. After adjustment for confounders, hypokalemia was independently associated with requiring IMV during the admission (OR 8.98, 95% CI 2.54–31.74). Mortality was 15.0% ($n = 46$) and was not influenced by low $K^+$. Hypokalemia was associated with longer hospital and ICU stays.
*Conclusions:* Hypokalemia is prevalent in patients with COVID-19 pneumonia. Hypokalemia is an independent predictor of IMV requirement and seems to be a sensitive biomarker of severe progression of COVID-19.

- ***Prevalence of hypocalcemia in COVID-19:***

- In April 2020, during the frst pandemic spread in Europe, a case of severe acute hypocalcemia in an Italian previously thyroidectomized patient with SARS-CoV-2 infection was reported . Therefore, COVID-19 was suggested for the frst-time as the possible precipitating cause of a subclinical post-surgical hypoparathyroidism.

- Interestingly, previous studies, conducted in 2003 and 2016 and focused on SARS and Ebola past epidemic emergencies, reported hypocalcemia as a highly prevalent biochemical abnormality in patients affected.

- Most of the available studies evaluated total serum calcium levels, adjusted or not for albumin levels, defning hypocalcemia as levels below either 2.2 mmol/L (8.8 mg/dL) or 2.15 mmol/L (8.6 mg/dL) or 2.12 mmol/L (8.5 mg/dL), reporting a hypocalcemia prevalence ranging from 62.6% to 74.7% (20–30).
- Other studies evaluating ionized serum calcium levels reported a hypocalcemia prevalence higher than 80%.

- To date, several potential factors have been hypothesized to play a role in determining hypocalcemia in COVID-19.
- Among them, we will shortly review calcium dependent viral mechanisms of action:
- High prevalence of hypovitaminosis D in general population
- chronic and acute malnutrition during critical illness
- High levels of unbound and unsaturated fatty acids (UFA) in infammatory responses.

- COVID-19 extra-pulmonary manifestations include systemic and difuse hematologic and thrombotic complications .
- Symptomatic acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism were reported in up to 30% of patients .
- Calcium ion plays a fundamental role in coagulation, platelet adhesion, contractility of myocardial and smooth muscle cells.

- Confrming a possible strict relationship between hypocalcemia and coagulopathy, D-dimer levels and prothrombin activity were reported higher in hypocalcemic compared to normocalcemic COVID-19 patients .

- Strongly negative correlation was found between serum calcium and D-dimer levels.

- Several authors contributed to a better understanding of hypocalcemia in COVID-19 underlying diverse possible pathophysiological mechanisms.

- In view of the dimensions of the observed phenomenon, it is likely that multiple mechanisms could underlie a so widespread fnding in COVID-19 patients, a quite heterogenous population with diferent degree of severity, clinical background and disease outcomes

- Ca2+has been involved in almost every step of viral life-cycles, regulating virion structure formation, virus cell entry, viral gene expression, post-translational processing of viral proteins and virion maturation and release.
- How this heavily calcium-dependent SARS-CoV-2 mechanism of action may afect serum calcium levels is yet unknown.
- However, it can be hypothesized that disruption in calcium homeostasis in patients with severe infection and high viral load may cause calcium depletion from blood circulation.

- Magnesium, an essential mineral for basic biochemical reactions, participates in a cluster of normal physiological functions and metabolism, such as the transport of potassium and calcium ions across cell membranes , energy metabolism, protein and nucleic acid synthesis.

- Among its various functions, magnesium has an anti-inflammatory action, and plays a role in the immune response, antioxidant protection, and vasodilation .

**Table 1: Reasons why Magnesium and Vitamin D Deficiency may lead to Immune Dysfunction, Cytokine Storm and Disseminated Intravascular Coagulation in COVID-19 patients**

| |
|---|
| Low intracellular free magnesium levels in NK and $CD8^+$ T cells reduces their cytotoxicity. |
| Patients with genetically low intracellular free magnesium, who are supplemented with magnesium, have a partial or near complete reversal of dysfunctional NK and $CD8^+$ T cells and a reduced viral load. |
| Dysfunctional $CD8^+$ T cell cytotoxicity leads to increased proinflammatory death in virally infected cells and healthy bystander cells, as opposed to silent apoptotic death, increasing the risk of cytokine storm in the lungs. |
| Magnesium activates vitamin D into the hormone calcitriol. |
| Active vitamin D is required to boost the expression of cathelicidins. |
| Magnesium deficiency slows fibrinolysis and increases coagulation and thrombosis. |
| Low magnesium status increases damage to tissues and cellular membranes and reduces antioxidant defense systems leading to increased oxidative stress and damage. |
| Magnesium deficient animals have a depressed immune response.[45] |

- Hypomagnesemia is commonly seen (ICU) patients and appears associated with greater risk of mortality, sepsis, mechanical ventilation, and the length of ICU stay.
- . In ICU, a retrospective study shows that patients with hypermagnesemia at admission were at two-fold increased crude risk for death than those with normal levels.
- Lastly, in community-acquired pneumonia, high normal magnesium levels (between 0.82-0.99 mmol/L) have been correlated with higher 30-day mortality rates.

- In a large cohort of 65,974 patients  hospitalized in the Mayo Clinic, hypermagnesemia had the most independent influence on worse patient outcomes.

- Reduced survival was noted in patients with both low and high magnesium levels. The highest magnesium range (>0.95 mol/L), however, was the strongest independent predictor of hospital mortality.

- During coronavirus disease 2019 (Covid-19), hypomagnesemia could have serious implications and possibly lead to progress from mild form to a severe outcome of the disease.

- In fact, magnesium deficiency may induce a drop of T cells, increase plasma concentration of inflammatory cytokines, and endothelial dysfunction.

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# Dysmagnesemia in Covid-19 cohort patients: prevalence and associated factors

**Didier Quilliot[1], Olivier Bonsack[1], Roland Jaussaud[2], André Mazur[3]**

*[1] Transversal Nutrition Unit and; [2] Internal Medicine and Clinical Immunology. Nancy University Hospital, University of Lorraine, France; [3] Université Clermont Auvergne, INRAE, UNH, Unité de Nutrition Humaine, Clermont-Ferrand, France*

**Correspondence**

<d.quilliot@chru-nancy.fr>

**Abstract.** Hypomagnesemia and hypermagnesemia could have serious implications and possibly lead to progress from a mild form to a severe outcome of Covid-19. Susceptibility of subjects with low magnesium status to develop and enhance this infection is possible. There is little data on the magnesium status of patients with Covid-19 with different degrees of severity. This study was conducted to evaluate prevalence of dysmagnesemia in a prospective Covid-19 cohort study according to the severity of the clinical manifestations and to identify factors associated.
Serum magnesium was measured in 300 of 549 patients admitted to the hospital due to severe Covid-19. According to the WHO guidelines, patients were classified as moderate, severe, or critical. 48% patients had a magnesemia below 0.75 mmol/L (defined as magnesium deficiency) including 13% with a marked hypomagnesemia (<0.65 mmol/L). 9.6% had values equal to or higher than 0.95 mmol/L. Serum magnesium concentrations were significantly lower in female than in male ($0.73 \pm 0.12$ vs $0.80 \pm 0.13$ mmol/L), whereas the sex ratio M/F was higher in severe and critical form ($p<0.001$). In a bivariate analysis, the risk of magnesium deficiency was significantly and negatively associated with infection severity ($p<0.001$), sex ratio (M/F, $p<0.001$), oxygenotherapy ($p<0.001$), stay in critical care unit ($p=0.028$), and positively with nephropathy ($p=0.026$). Logistic regression analysis revealed that the strongest predictors of magnesium deficiency were female sex (OR=2.67, $p<0.001$) and nephropathy (OR=2.12, $p=0.032$) and after exclusion of sex ratio, the severity of infection (OR=0.46, $p=0.04$ and OR=0.39 $p=0.01$), for critical and moderate forms, respectively. This transversal study reveals a high prevalence of hypomagnesemia in hospitalized patients for Covid-19, while high-level serum magnesium concentration was more prevalent in critical form.

Original Investigation

Kidney360

# Increased Mortality Associated with Hypermagnesemia in Severe COVID-19 Illness

Jacob S. Stevens [1,2], Andrew A. Moses[1], Thomas L. Nickolas[1,2], Syed Ali Husain[1,2], and Sumit Mohan[1,2,3]

**Methods** We retrospectively identified all patients with a positive test result for SARS-CoV-2 who were admitted to a large quaternary care center in New York City in spring 2020. Details of the patients' demographics and hospital course were obtained retrospectively from medical records. Patients were defined as having hypermagnesemia if their median magnesium over the course of their hospitalization was >2.4 mg/dl.

**Results** A total of 1685 patients hospitalized with COVID-19 had their magnesium levels checked during their hospitalization, and were included in the final study cohort, among whom 355 (21%) had hypermagnesemia. Patients who were hypermagnesemic had a higher incidence of shock requiring pressors (35% vs 27%, $P<0.01$), respiratory failure requiring mechanical ventilation (28% vs 21%, $P=0.01$), AKI (65% vs 50%, $P<0.001$), and AKI severe enough to require renal replacement therapy (18% vs 5%, $P<0.001$). In an adjusted multivariable model, hypermagnesemia was observed more commonly with increasing age, male sex, AKI requiring RRT, hyperkalemia, and higher CPK. Survival probability at 30 days was 34% for the patients with hypermagnesemia, compared with 65% for patients without hypermagnesemia. An adjusted multivariable time to event analysis identified an increased risk of mortality with older age, need for vasopressors, higher C-reactive protein levels, and hypermagnesemia (HR, 2.03; 95% CI, 1.63 to 2.54, $P<0.001$).

**Conclusions** In conclusion, we identified an association between hypermagnesemia among patients hospitalized with COVID-19 and increased mortality. Although the exact mechanism of this relationship remains unclear, hypermagnesemia potentially represents increased cell turnover and higher severity of illness, which is frequently associated with more severe forms of AKI.