

Serum magnesium levels in hospitalized patients with SARS-CoV-2

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ABSTRACT

Early studies have reported various electrolyte abnormalities at admission in patients with severe COVID-19. 104 out of 193 patients admitted to our institution presented with hypermagnesemia at presentation. It is believed this may be important in the evaluation of severe SARS-CoV-2 infections. This study evaluated the outcomes of hypermagnesemia in patients with COVID-19. A retrospective chart review of patients admitted to the hospital with confirmed SARS-CoV-2 infection was conducted. A review of the medical literature regarding hypermagnesemia, magnesium levels in critical care illness and electrolyte abnormalities in patients with COVID-19 was performed. Differences in demographic and clinical characteristics of patients with hypermagnesemia and normomagnesemia were evaluated using descriptive statistics. Other known variables of disease severity were analyzed. 104 patients (54%) were identified with hypermagnesemia (≥ 2.5 mg/dL). 48 of those patients were admitted to the intensive care unit (46%, $p < 0.001$). 34 patients required ventilator support (32%, $p < 0.0001$). With age-adjusted logistic regression analysis hypermagnesemia was associated with mortality ($p = 0.007$). This study demonstrates that hypermagnesemia is a significant marker of disease severity and adverse outcome in SARS-CoV-2 infections. We recommend serum magnesium be added to the panel of tests routinely ordered in evaluation of severe SARS-CoV-2 infections.

INTRODUCTION

In early COVID-19 studies evidence has been elucidated that electrolyte disorders may be present at presentation. This includes hyponatremia, hypokalemia and hypocalcemia.¹ The noted electrolyte abnormalities have important implications for patient care.¹

Hypermagnesemia is an uncommon electrolyte disorder found largely in patients with renal failure.² Approximately 10% of filtered magnesium is absorbed in the proximal tubule. Most of the filtered magnesium is reabsorbed in the loop of Henle.^{3,4} Hypermagnesemia has been associated with increased mortality in critical illness.^{5–13} In the course of care of 193 eligible SARS-CoV-2 infections admitted to Kern Medical, one of the coauthors (GP) noted an

Significance of this study

What is already known about this subject?

- ▶ Hypermagnesemia has previously been associated with morbidity and mortality in critical care patients who do not have SARS-CoV-2.

What are the new findings?

- ▶ We have found that hypermagnesemia is an excellent predictor of morbidity and mortality in people with significant SARS-CoV-2 infections.

How might these results change the focus of research or clinical practice?

- ▶ Serum magnesium should be a routine of the intake of patients with SARS-CoV-2 at least in those who require hospitalization.

increase in serum magnesium (Mg^{++}) that was not attributable to renal failure or oral magnesium ingestion as being a frequent correlate of severity. The hypothesis of this study is that hypermagnesemia is associated with severity of illness and death.

METHODS

A review of the medical literature using SARS-CoV-2, COVID-19 and serum magnesium was queried. PubMed, Google Scholar and Research Gate were searched. Reference lists of included articles and related reviews were manually searched.

Study design

This is a retrospective cohort study of patients with confirmed COVID-19 pneumonia hospitalized in an academic medical center in California. The study period was from March 13, 2020 to February 2, 2021.

The diagnosis of COVID-19 required a positive real transcriptase PCR test for SARS-CoV-2 using the Aptima SARS-CoV-2 Assay (Panther System). Inmates, pregnant women, children less than 18 years of age, ambulatory patients and patients with serum creatinine ≥ 1.21 mg/dL were excluded from this study (figure 1). Other than the excluded individuals mentioned above, records of all admitted patients with



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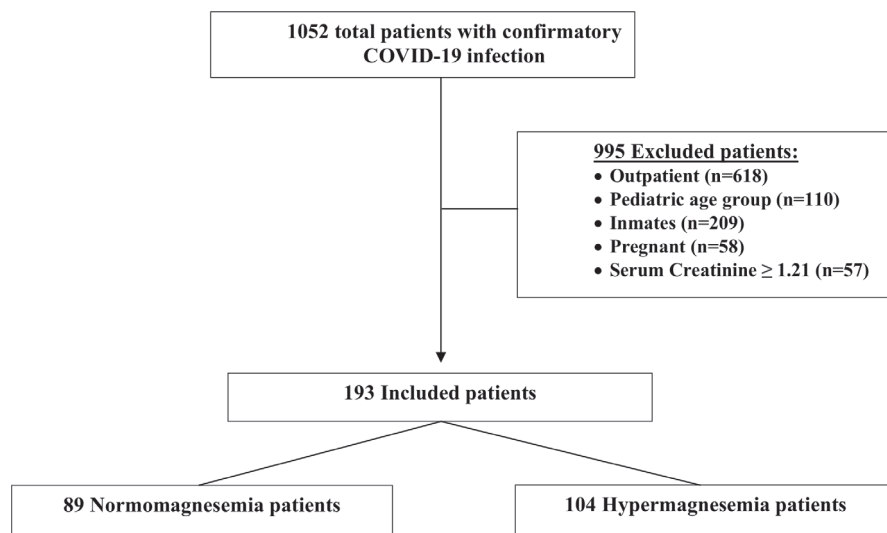


Figure 1 Study cohort (study baseline was defined as the time of admission).

COVID-19 pneumonia diagnosed according to WHO interim guidance were evaluated.¹⁴ Criteria for hospital admission included poor clinical status, hypoxemia on room air (oximetry $<94\%$), and/or significant radiological pulmonary opacities. Patient treatment varied during this time period based on evolving protocols.

Data collection

Demographics, signs and symptoms and comorbidities (diabetes mellitus, hypertension, cardiac disease, respiratory disease, liver disease, malignancy, immunosuppression, dyslipidemia) as noted in the electronic medical record were included. Laboratory data including serum magnesium, serum creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, D-dimer, lactate dehydrogenase (LDH) and procalcitonin were registered from the time of admission. Specific therapeutic agents (remdesivir, dexamethasone, convalescent plasma) were documented. Required respiratory support including nasal cannula, respiratory mask, high-flow nasal cannula and invasive mechanical ventilation was recorded. Level of care medical-surgical unit versus intensive care unit (ICU) was noted. Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) scores were calculated and evaluated for the 2 study groups.

Statistical analysis

Statistical analysis was conducted with Stata V.15.0. Baseline characteristics of patients were summarized using descriptive statistics. Continuous variables were indicated as mean and SD and categorical variables as numbers. The distribution of demographic and clinical characteristics across our exposure groups was calculated using t-test (for continuous variables) and χ^2 and Fisher's exact tests (for categorical variables). Univariate and multivariable logistic regression models were used to assess the impact of Mg^{++} levels on risk of death and generate respective ORs and 95% CIs. Cox regression models were used to further study the association of baseline Mg^{++} with time to death. Kaplan-Meier

curves were plotted (figure 2). A p value <0.05 was considered statistically significant.

Outcomes

The outcomes of this study are as follows: length of hospital stay, admission to ICU, ventilator requirement and death.

RESULTS

Between March 13, 2020 and February 2, 2021, a total of 794 patients tested positive for SARS-CoV-2 at Kern Medical. Nine hundred and ninety-five were excluded (618 did not require hospitalization, 209 inmates, 110 pediatric patients, 58 pregnant patients and 57 patients with serum creatinine ≥ 1.21 mg/dL¹⁵ at presentation) (figure 1). One hundred and ninety-three patients met study eligibility. The patients were then classified into groups according to the magnesium level at the time of admission: hypermagnesemia, Mg^{++} level ≥ 2.5 mg/dL and normomagnesemia, Mg^{++} level <2.5 mg/dL (>1.7 mg/dL).

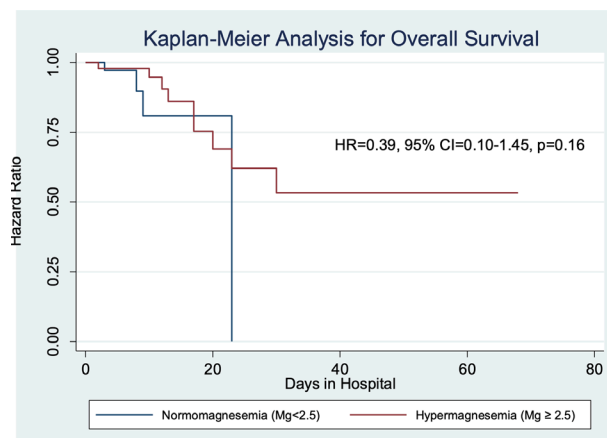


Figure 2 Kaplan-Meier curves for the association of baseline Mg^{++} with overall mortality.

Table 1 Demographic and clinical characteristics, comorbidities and inflammatory markers of patients according to baseline magnesium levels*

Characteristics	Total	Normomagnesemia Mg <2.5 n=89	Hypermagnesemia Mg ≥2.5 n=104	P value
Age, years: mean (SD)	193	53 (17)	53 (15)	
Male sex: n (%)	108	48 (54)	60 (58)	0.66
Race: n (%)				
Latinx	166	72 (81)	94 (90)	0.02
Caucasian	13	10 (11)	3 (3)	
African American	8	6 (7)	2 (2)	
Other	6	1 (1)	5 (5)	
BMI, kg/m ² : mean (SD)	193	33.62 (11)	32.95 (8.20)	0.62
<30	86	39 (44%)	47 (45%)	0.84
≥30	107	50 (56%)	57 (55%)	
Serum creatinine: mean (SD)	193	0.73 (0.20)	0.73 (0.18)	0.80
Signs and symptoms: n (%)				
Fever (subjective)	143	59 (66)	84 (81)	0.02
Dyspnea	160	65 (73)	95 (91)	0.001
Cough	150	61 (69)	89 (86)	0.005
Diarrhea	40	21 (24)	19 (18)	0.36
Anosmia	8	6 (7)	2 (2)	0.14
Dysgeusia	16	11 (12)	5 (5)	0.06
Comorbidities: n (%)				
Diabetes mellitus	86	42 (47)	44 (42)	0.50
Hypertension	85	40 (45)	45 (43)	0.82
Cardiac disease	26	12 (13)	14 (13)	0.99
Respiratory disease	17	8 (9)	9 (9)	0.93
Liver disease	9	6 (7)	3 (3)	0.21
Malignancy	19	9 (10)	10 (10)	0.91
Immunosuppression	8	5 (6)	3 (3)	0.34
Dyslipidemia	34	16 (18)	18 (17)	0.90
Vital signs: mean (SD) at presentation				
Temperature	193	38.02 (0.92)	38.38 (0.88)	0.001
Oxygen saturation %	193	86.5% (13%)	80% (14%)	0.001
APACHE II score	60	13.91 (5.35)	16.85 (6.35)	0.15
Inflammatory markers: mean (SD)				
CRP	173	11.48 (8.02)	15.57 (9.20)	0.002
ESR	171	57.06 (29.97)	76.60 (24.20)	<0.0001
Ferritin	165	499.14 (435)	1094.27 (1149)	<0.0001
D-dimer	153	1395.43 (1239)	2075.78 (1586)	0.005
LDH	160	365.64 (303)	470.77 (227)	0.01
Procalcitonin	175	0.38 (1.38)	1.80 (7)	0.06

Results displayed in bold highlight the clinical characteristics which reached statistical significance.

*A p value <0.05 is used for statistical significance. T-test was used for comparison of continuous variables whereas χ^2 and Fisher's exact tests were used for categorical variables. Signs and symptoms: numbers represent patients who reported these symptoms. Laboratory values and signs and symptoms were abstracted through chart review. Total n represents available data from all patients.

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

Baseline Mg++ level of patients who met the inclusion criteria was 2.44 mg/dL (SD: 0.36). One hundred and four (54%) of our patients had hypermagnesemia (≥2.5 mg/dL) and 89 (46%) had normomagnesemia (<2.5 mg/dL). The records of the 104 patients with elevated serum magnesium did not contain evidence of magnesium supplementation or renal dysfunction.

The median age of the study population was 54 years (IQR: 41–65) in the hypermagnesemia group and 53 years (IQR: 40–65) in normomagnesemia group. The majority of our participants were male (108, 56%) and of Latinx ethnicity (n=166, 86%). Presenting symptoms included subjective fever, dyspnea, cough, anosmia, dysgeusia and diarrhea. Ninety-one per cent of patients with

Table 2 Distribution of oxygenation requirement, level of care unit and outcomes according to baseline magnesium levels

	Total	Normomagnesemia Mg <2.5	Hypermagnesemia Mg ≥2.5	P value
Oxygenation*, n (%)				
Nasal cannula	54	29 (33)	25 (24)	0.18
Ventilator	35	1 (1.12)	34 (33)	<0.0001
Other†	59	26 (29)	33 (32)	0.71
Therapy, n (%)				
Remdesivir	75	29 (33)	46 (45)	0.09
Dexamethasone	134	46 (52)	88 (85)	<0.0001
Convalescent plasma	120	52 (58)	68 (65)	0.32
Level of care unit and outcomes‡, n (%)				
MedSurg	132	76 (85)	56 (54)	<0.001
ICU	61	13 (15)	48 (46)	<0.001
Death	24	6 (7)	18 (17)	0.03
Days in hospital	87	6.7 (4)	15.42 (13)	0.001
Days in ICU	40	6.18 (5)	14.55 (11)	0.03
Logistic regression analysis§				
	Univariate OR (95% CI)	P value	Multivariable adjusted OR (95% CI)	P value
Death	2.89 (1.10 to 7.65)	0.03	5.39 (1.59 to 18.28)	0.007

X² and Fisher's exact tests were used for categorical variables. Total n represents available data from all patients.

Results displayed in bold highlight the requirement of ventilator and outcomes which reached statistical significance.

*A p value <0.05 is used for statistical significance. T-test is used for comparison of continuous variables.

†Other is defined as use of high-flow nasal cannula, respiratory mask and bilevel positive airway pressure (BiPAP).

‡A p value <0.05 is used for statistical significance. Multivariable model adjusted for age, gender, race and overall comorbidity burden (sum of 8 comorbidities above).

§Death (outcome) was assessed from chart review. Age-adjusted analysis using logistic regression analysis (age at admission).

ICU, intensive care unit; MedSurg, (medical-surgical) admission into the inpatient unit.

hypermagnesemia had dyspnea at presentation ($p=0.001$). This compares to 73% among patients with normomagnesemia. Eighty-six per cent in the hypermagnesemia group presented with cough ($p=0.005$) compared with 69% with normomagnesemia. Patients with hypermagnesemia had significantly lower oxygen saturation on room air (80%, $p=0.001$) at presentation compared with patients with normomagnesemia (87%). Significantly more patients with hypermagnesemia received dexamethasone and supplemental oxygen (table 1).

Patients with hypermagnesemia had significantly higher levels of CRP, ESR, D-dimer, ferritin and LDH. The number of bacterial coinfections as indicated by procalcitonin elevation was low in the study population and was not significantly different between study groups.

Mean duration of admission to hospital was 11.41 days (SD: 10.7) with 15.42 days in the hypermagnesemia group and 6.7 days in normomagnesemia group, $p=0.0001$. Patients with hypermagnesemia were found to have a higher probability of being admitted to ICU. Forty-eight per cent of patients with hypermagnesemia were admitted into ICU versus 15% with normomagnesemia ($p<0.001$) (table 1). Thirty-four of 35 patients who required a ventilator had hypermagnesemia at presentation ($p<0.0001$). With age-adjusted logistic regression analysis hypermagnesemia was associated with mortality ($p=0.007$).

We further performed logistic regression models to assess the association of baseline magnesium with risk of death. Multivariate analysis adjusted for age, gender,

race and overall comorbidity burden including diabetes mellitus, hypertension, cardiac disease, respiratory disease, liver disease, malignancy, immunosuppression, and dyslipidemia was calculated. There was no significant difference in APACHE II scores in-between those with hypermagnesemia and normomagnesemia. Patients with hypermagnesemia had higher odds of ICU admission (OR=8.37, 95% CI 3.63 to 19.27, $p<0.0001$) and death (OR=5.39, 95% CI 1.59 to 18.28, $p=0.007$), respectively (table 2).

DISCUSSION

In previous studies, hypermagnesemia has been observed in critically ill patients, and an association between this alteration and mortality has been noted.^{7 8 12 13 16} Although the importance of magnesium is widely acknowledged, serum magnesium concentrations are not routinely determined in clinical medicine. Hence, magnesium is frequently referred to as the 'forgotten' cation.¹⁷ The Department of Medicine at Kern Medical has commonly ordered serum magnesium on admitted patients. All department of medicine admitted patients with COVID-19 had this test performed.

Thus far, despite the already extensive literature available on COVID-19 and its related biomarkers of activity and prognosis, no data are yet available on Mg++ levels in SARS-CoV-2 infection. Based on the search strategy in the Methods section this appears to be the first study that revealed a high incidence of hypermagnesemia in a

population of patients with SARS-CoV-2 at initial hospital evaluation.

Mg⁺⁺ is the second most abundant intracellular cation and is a cofactor in many enzymatic reactions including those involving energy metabolism.¹⁸ Ninety-nine per cent of the Mg⁺⁺ is stored intracellularly and less than 1% is in serum.^{19–21} In individuals with SARS-CoV-2 there are complexities of cellular injury including the kidney which may result in the release of Mg⁺⁺ from the intracellular compartment to extracellular compartment. Mg⁺⁺ metabolism is tightly regulated by a balanced interplay between intestinal absorption, renal reabsorption and renal excretion under normal conditions.

The intestinal absorption of Mg⁺⁺ involves a saturable (transcellular) active pathway and a non-saturable (paracellular) passive pathway. Paracellular Mg⁺⁺ absorption occurs by simple diffusion involving the transport of Mg⁺⁺ through epithelial tight junctions (TJ) and is responsible for 80%–90% of Mg⁺⁺ uptake.^{22–23} It is doubted that hypermagnesemia in our patients is due to increased intestinal absorption.

Our current knowledge of Mg⁺⁺ metabolism might suggest that CLDN 16 and CLDN 19 in the thick ascending limb of the loop of Henle play a critical role in hypermagnesemia.^{22–24} However, in a study by Tian *et al*, it is found that a large number of proteins involved in TJ formation and cell-cell adhesion junctions were drastically downregulated in patients with SARS-CoV-2, including CLDN 19.²⁵ Therefore, this is not a tenable hypothesis.

Dai *et al* reported that Mg⁺⁺ uptake in the distal convoluted tubule is concentration and voltage dependent. Peptide hormones such as parathyroid hormone (PTH), calcitonin, glucagon, and arginine vasopressin/antidiuretic hormone (ADH) enhance Mg⁺⁺ absorption in the distal tubule²⁶ (figure 3). The literature search undertaken as described above was unable to find evidence in our literature search for a role of PTH, calcitonin and glucagon in altered magnesium metabolism in SARS-CoV-2 infection.

This study has several limitations. It is a single-center retrospective design with a relatively small sample size. The exact mechanism of hypermagnesemia was not tested. The results therefore are hypothesis generating, and the exact mechanisms of hypermagnesemia should be tested by more fundamental experiments. The values of serum magnesium were of total magnesium rather than ionized magnesium. Total magnesium may not precisely reflect extracellular Mg⁺⁺.

In summary, this study suggests that hypermagnesemia is a marker of disease severity in hospitalized patients with SARS-CoV-2. Our data reflect increased length of stay, increased ICU admission, increased requirement for ventilator and death. It is suggested that serum magnesium should be added to the panel of tests routinely ordered in evaluation of significant SARS-CoV-2 infections. The hypermagnesemia may be a marker of a disease severity rather than a direct cause of morbidity and mortality. Further studies, both clinical and basic science, on hypermagnesemia associated with SARS-CoV-2 infections would appear to be warranted.

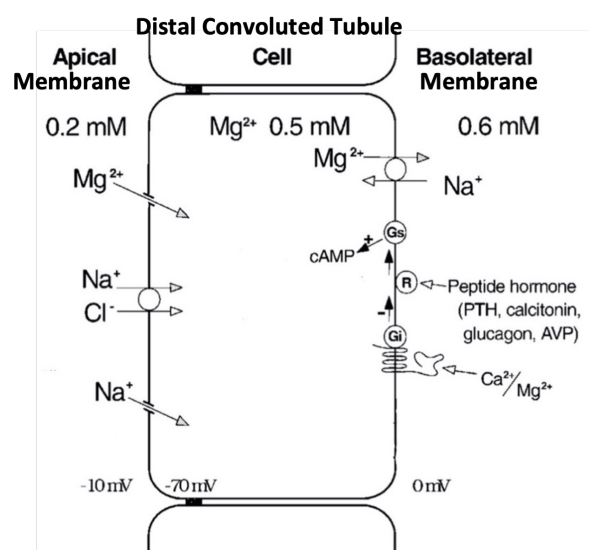


Figure 3 Schematic model of magnesium absorption in the distal convoluted tubule (DCT) cell. Peptide hormones such as parathyroid hormone (PTH), calcitonin, glucagon, and arginine vasopressin (AVP) enhance magnesium reabsorption in the DCT. The cellular mechanisms of these hormones are unknown but appear to involve, in part, stimulation of cAMP release and activation of protein kinase A, phospholipase C, and protein kinase C²⁶ (adapted from Dai *et al* [26]).

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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