

Original Article: Relationship between hypomagnesemia and mortality in critically ill patients admitted to the intensive care unit

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ABSTRACT

Background: Magnesium is a vital intracellular ion, with abnormalities in its levels linked to severe complications across various organ systems. Hypomagnesemia is observed in 7-11% of ICU patients. This study investigates the association between hypomagnesemia and mortality rates in critically ill patients.

Methods: This cross-sectional study included 80 critically ill patients admitted to the ICU at Sina and Al-Zahra hospitals, Tabriz. Serum magnesium levels were measured, and patient outcomes were analyzed based on SOFA, APACHE, and NUTRIC scores, ICU length of stay, mechanical ventilation needs, and 28-day mortality.

Results: A significant association was observed between low magnesium levels and poor outcomes. Patients with serum magnesium levels below 1.7 mg/dL had higher mortality rates, longer ICU stays, and increased mechanical ventilation requirements. Higher SOFA, APACHE, and NUTRIC scores were linked to lower magnesium levels, and patients with SOFA scores above 8.5 had an increased risk of mortality during hospitalization. Magnesium levels above 1.7 mg/dL correlated with better outcomes and shorter ICU stays.

Conclusion: Hypomagnesemia is associated with increased ICU mortality and adverse outcomes, highlighting the need for magnesium monitoring in critically ill patients. Further research with larger sample sizes is recommended to better understand magnesium's role in ICU patient management.

Introduction

The Hypomagnesemia, a state of abnormally low serum magnesium levels, is increasingly recognized as a common and clinically significant electrolyte disturbance in critically ill patients, particularly those in the

intensive care unit (ICU) [1-3]. Magnesium, an essential mineral and cofactor in over 300 enzymatic reactions, plays a vital role in numerous physiological processes, including neuromuscular transmission [4-6], myocardial contraction, blood pressure regulation, and glucose metabolism. Beyond its biochemical

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importance, magnesium's role in modulating inflammatory responses, maintaining vascular tone, and influencing cellular energy production makes its regulation critical for critically ill patients. Hypomagnesemia has been implicated in adverse clinical outcomes across a variety of critical conditions, potentially affecting morbidity and mortality rates in ICU settings. Despite this association, the relationship between hypomagnesemia and mortality among critically ill patients remains complex, and understanding this link is essential for advancing patient care in the ICU [7-9].

Magnesium depletion in critically ill patients can result from several mechanisms, including gastrointestinal losses, renal excretion, metabolic stress, and certain medications. Conditions such as sepsis, diabetic ketoacidosis, and major surgeries are commonly associated with increased magnesium losses. In the ICU, the frequent use of medications like diuretics, proton pump inhibitors, and nephrotoxic antibiotics further compounds the risk of hypomagnesemia [10-12].

Additionally, the high prevalence of malnutrition in critically ill patients, particularly those with prolonged ICU stays or comorbidities like chronic kidney disease, also predisposes them to magnesium deficiency [13-15].

Given magnesium's role in cellular homeostasis and its effect on other electrolytes such as potassium and calcium, hypomagnesemia can lead to a cascade of complications, including arrhythmias, hypertension, and poor immune responses, thereby increasing the risk of adverse outcomes [16-18].

Previous research has shown variable associations between hypomagnesemia and mortality in the ICU, with some studies highlighting a strong link and others suggesting no significant effect. The inconsistency may stem from differences in patient populations, ICU settings, definitions of hypomagnesemia, and treatment protocols [19-21]. Studies have also

documented the association of hypomagnesemia with specific types of mortality, such as those related to cardiovascular events, respiratory failure, and sepsis. Patients with cardiac conditions, for instance, may experience exacerbated outcomes if hypomagnesemia-induced arrhythmias occur. Similarly, those with respiratory issues may be at a higher risk due to magnesium's involvement in respiratory muscle function. This variability underscores the need for further investigation into hypomagnesemia's role in ICU mortality and the factors that might modify this relationship, such as underlying health conditions, ICU interventions, and patient demographics [22].

Beyond the association with mortality, hypomagnesemia in ICU patients has been linked to other critical outcomes, such as prolonged mechanical ventilation, increased length of ICU stay, and higher rates of infection. These associations emphasize the broader implications of hypomagnesemia in ICU management, as they may contribute to resource utilization and patient quality of life post-discharge [23].

Early identification and correction of hypomagnesemia could, therefore, potentially reduce complications, ICU length of stay, and healthcare costs, all of which have significant implications for health systems worldwide. However, the optimal approach to magnesium monitoring and supplementation in critically ill patients remains undefined. While magnesium supplementation is a common ICU intervention, its effectiveness and safety in reducing mortality are still under debate, given the potential for adverse effects, such as hypotension and bradycardia, in rapid or excessive replacement. Understanding the pathophysiological role of magnesium in critically ill patients, as well as the specific outcomes associated with hypomagnesemia, is essential for refining clinical guidelines [24-26].

To improve patient outcomes, it is crucial to establish a standardized approach to magnesium monitoring and management in the ICU. Clinical practice varies widely, with some institutions implementing routine magnesium monitoring and others adopting a more selective approach [27-29].

Additionally, the variability in target serum magnesium levels and supplementation practices poses a challenge in developing universally accepted protocols. Emerging studies suggest that a serum magnesium level within a higher range of normal might be protective in critical illness, but further randomized trials are necessary to validate these findings and clarify the benefits of magnesium supplementation on mortality and morbidity in ICU populations [30].

This study aims to examine the relationship between hypomagnesemia and mortality in critically ill patients admitted to the ICU. By analyzing mortality outcomes in relation to serum magnesium levels upon admission and throughout ICU stay, this research seeks to provide insights into whether hypomagnesemia serves as an independent risk factor for mortality or if it is merely a marker of severity of illness. Additionally, the study will investigate secondary outcomes, including the length of ICU stay, need for mechanical ventilation, and incidence of infections, to better understand hypomagnesemia's broader impact on critically ill patients. Findings from this study could inform clinical practice guidelines on magnesium management, potentially leading to improved interventions that enhance patient survival and recovery in the ICU [31-33].

Material and methods

Study Design: This study is a cross-sectional analysis conducted over 17 months at Tabriz University of Medical Sciences. The target sample size was calculated using Cochran's

formula for a finite population, aiming for a 5% error margin and 80% predictive power, resulting in a sample size of 80 patients. Patients were selected randomly based on their admission times and available case numbers over the specified study period.

Sampling and Sample Size Calculation: The sample size for this study was determined using Cochran's formula for a finite population, aiming for a 5% margin of error and 80% power. Based on similar data from the previous year and the ICU admission rate, the required sample size was calculated to be 80 patients. Random sampling was employed, selecting patients admitted over the 17-month study period based on their admission timing and available case numbers, ensuring a representative distribution across the study period.

Inclusion Criteria: Patients eligible for inclusion were those admitted to the ICU for a minimum of 48 hours, aged over 12 years, and who provided informed consent or had consent from a legal representative.

Exclusion Criteria: Exclusion criteria included patients with a history of magnesium supplement intake, ICU stays shorter than 48 hours, confirmed renal failure, known neuromuscular diseases, and those who declined participation.

Procedures: Upon obtaining approval from the ethics committee of Tabriz University of Medical Sciences, eligible patients admitted to Sina Hospital's ICU from March 2019 to July 2020 were included. Demographic data, APACHE, NUTRIC, and SOFA scores, comorbidities, serum magnesium levels, vasopressor use, renal replacement therapy (RRT) involvement, and ICU outcomes were recorded for each patient. APACHE, NUTRIC, and SOFA scores were calculated based on validated scoring systems.

Patients received a standard ICU infusion of 3.5 grams of magnesium sulfate over six hours unless contraindicated due to renal failure or neuromuscular diseases. Data collection included vasopressor use, 28-day mortality, albumin and calcium levels, ICU stay length, days on invasive ventilation, comorbidities (e.g., sepsis, diabetes), and medication history.

Statistical Analysis: Continuous variables are presented as mean $\pm$ standard deviation. Logistic regression was applied to evaluate associations between potential predictors and primary outcomes. Odds ratios and 95% confidence intervals were calculated to identify independent predictors of initial clinical severity. ROC curves were generated for APACHE, SOFA, and NUTRIC scores, with the Youden index used to determine optimal cut-off values for patient severity classification. A p-value <0.05 was considered statistically significant.

Ethical Considerations: This study was conducted following approval from the Ethics Committee of Tabriz University of Medical Sciences (Approval ID: IR.TBZMED.REC.1399.618). Informed consent was obtained from all patients or their legal representatives. Confidentiality was maintained throughout and after the study. Given that single-dose magnesium sulfate infusion is part of standard ICU practice for its antioxidant, anti-apoptotic, analgesic, and anticonvulsant properties, the study posed no risk of depriving patients of standard care, added treatments, or additional financial burdens. Magnesium checks were part of routine ICU admission assessments for all patients.

Results

Descriptive Analysis

Initial descriptive statistics were calculated for all variables, including count, mean, standard deviation, standard error, skewness, kurtosis, minimum, maximum, and both absolute and relative frequencies.

Table 1. Descriptive Statistics of Parametric Variables in the Study Population

Variable	Mean	SD	SE	Skewness	Kurtosis	Min	Max	Count
Age (years)	54.02	18.85	2.10	-0.234	-0.634	15	93	80
APACHE	16.16	10.22	1.14	0.200	-1.267	0	36	80
SOFA	6.30	4.52	0.50	0.318	-0.917	0	18	80
NUTRIC	3.35	2.43	0.27	0.289	-1.010	0	9	80
Mg (mg/dL)	1.76	0.42	0.04	0.011	-1.010	0.9	2.6	80
Ca (mg/dL)	7.78	0.75	0.08	0.149	-0.173	6.0	9.6	80
Albumin (g/dL)	2.90	0.56	0.06	-0.216	-0.263	1.5	4.0	80
Mechanical Ventilation Duration (days)	4.63	8.88	0.99	3.62	18.63	0	60	80
ICU Stay (days)	10.81	9.53	1.06	2.40	8.37	2	60	80
Vasopressor Dose (mcg/kg/min)	7.85	2.98	0.65	0.476	-0.560	5	15	21
Vasopressor Infusion Duration (hours)	5.76	3.20	0.70	0.208	-1.44	1	10	21

Among the 80 patients, 39 were male and 41 were female, with 72.5% admitted to Sina

Hospital and the remainder to Al-Zahra Hospital. The mean age was 54.02 ± 18.85 years, with a

range of 15 to 93 years. Hypertension (HTN) and diabetes mellitus (DM) were the most common comorbidities, observed in 37.5% and 22.5% of patients, respectively.

Table 2. Frequency of Comorbidities

Comorbidity	Present (%)	Absent (%)
DM	22.5	77.5
HTN	33.75	66.25
HLP	5.0	95.0
IHD	13.75	86.25
Asthma/COPD	12.5	87.5
CVA	5.0	95.0
Alzheimer's/Parkinson's	7.5	92.5

Patients were categorized by ICU admission reason, with pulmonary diseases (27.5%) being the most frequent, followed by malignancies and obstetric cases (both at 16.5%).

Serum Magnesium Levels and Patient Outcomes

Upon admission, 42.5% of patients had serum magnesium levels below 1.7 mg/dL, while 53.75% had levels between 1.7 and 2.4 mg/dL. ICU outcomes showed that 65 patients were discharged, while 15 died. Among discharged patients, 9 succumbed within 28 days post-discharge.

Table 4. ICU Outcomes

Outcome	Discharged (%)	Deceased (%)
Initial Outcome	81.25	18.75
28-day Outcome	70.0	30.0

Using the ROC curve, a serum magnesium level of 1.620 mg/dL was identified as the optimal cutoff for initial ICU discharge prediction, with a sensitivity and specificity of 67.7% and 66.7%, respectively. For the 28-day post-discharge outcome, a cutoff of 1.645 mg/dL was

determined, with a sensitivity and specificity of 75.0%.

Correlation Analysis

Pearson's correlation analysis demonstrated a significant positive association between higher magnesium levels and lower mortality ($p < 0.01$). Additionally, higher magnesium levels were associated with shorter ICU stay and ventilation duration.

Discussion

Magnesium is an essential ion in the human body, recognized as the second most common intracellular cation, and its abnormalities can impact almost every organ system significantly. Hypomagnesemia has been reported in hospitalized patients with varying prevalence, with studies indicating rates between 7% and 11% in ICU patients [18-21†source]. This study aims to examine the association between hypomagnesemia and mortality rates in critically ill patients admitted to the ICU, providing evidence of the clinical importance of serum magnesium levels [34-36].

In a study by Safari and colleagues (2007), which retrospectively analyzed 100 ICU patients over 16 years of age (62 surgical and 38 medical) at Al-Zahra University Hospital, Isfahan, over two years [37-39], hypomagnesemic patients showed a higher prevalence of hypocalcemia, hypokalemia, and hyponatremia compared to patients with normal magnesium levels. Our findings align, as we also observed that higher magnesium levels correlated with elevated calcium and albumin levels, suggesting a physiological interdependence among these electrolytes [40-42].

Safari et al. further reported that a higher SOFA score was associated with a greater need for mechanical ventilation and prolonged ventilation duration among patients with hypomagnesemia. Mortality rates were notably higher in hypomagnesemic patients. Similarly, in our study, SOFA, APACHE, and NUTRIC scores decreased as serum magnesium levels rose, underscoring magnesium's potential role in predicting ICU outcomes [43-45]. Patients with SOFA scores above 8.5 faced a significantly higher in-hospital mortality risk, while those with scores above 5.5 were more likely to die within 28 days post-discharge [46].

The study by Ravi Kumar et al. (2008) conducted a prospective observational study in an Indian hospital ICU with 50 critically ill patients, finding higher mortality in the hypomagnesemic group compared to those with normal magnesium levels. In our study, we found that patients who survived (either after primary discharge or within 28 days post-discharge) had a significantly higher mean serum magnesium level compared to those who did not. Mortality rates were markedly elevated in patients with serum magnesium levels below 1.7 mg/dL, reaffirming hypomagnesemia as a risk factor for poor ICU outcomes [47].

A 2016 systematic review and meta-analysis by Sikarin Upala and colleagues included data from 20 complete articles and 6 studies covering 1550 patients, revealing that hypomagnesemia was associated with increased mortality, greater need for mechanical ventilation, and longer ICU stays. These associations were statistically significant in our study as well, validating the relevance of magnesium monitoring and supplementation in critically ill patients [48].

In contrast to Sunil et al. (2016), who observed no difference in ICU length of stay between hypomagnesemic and normomagnesemic patients in their study on 172 ICU patients in an Indian hospital, our findings diverged. We noted a significant reduction in ICU days as serum

magnesium levels increased, implying a potential role of magnesium supplementation in reducing ICU stay durations.

Conclusion

This study emphasizes the association between hypomagnesemia and increased mortality in critically ill patients admitted to the ICU. Lower serum magnesium levels were correlated with higher SOFA, APACHE, and NUTRIC scores, longer ICU stays, increased mechanical ventilation requirements, prolonged ventilation duration, and ultimately, a higher mortality rate. These findings support the consideration of serum magnesium as an important biomarker in assessing ICU patient outcomes.

Recommendations

Given these findings, further studies with larger sample sizes are recommended to explore the relationship between magnesium levels and other predictive factors of disease severity and mortality. Understanding these associations could enhance ICU protocols and improve patient management.

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