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ORIGINAL ARTICLE

Dysmagnesemia in Hospitalized Patients: Prevalence and Prognostic Importance

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Abstract

Objective: To examine the prevalence of serum magnesium (Mg) alterations and outcomes in hospitalized patients.

Patients and Methods: All admissions to Mayo Clinic in Rochester, Minnesota, from January 1, 2009, through December 31, 2013 (288,120 patients), were screened. Admission Mg from each unique patient and relevant clinical data were extracted from the institutional electronic database.

Results: After excluding patients aged less than 18 years, those without Mg measurement, and readmission episodes, a total of 65,974 patients were studied. Magnesium levels of 2.1 mg/dL or higher were found in 20,777 patients (31.5%), and levels less than 1.7 mg/dL were noted in 13,320 (20.2%). Hypomagnesemia was common in patients with hematologic/oncological disorders, and hypermagnesemia was common in those with cardiovascular disease. The lowest hospital mortality, assessed by restricted cubic spline and percentage death, occurred in patients with Mg levels between 1.7 and 1.89 mg/dL. An Mg level of less than 1.7 mg/dL was independently associated with an increased risk of hospital mortality after adjusting for all variables except the admission diagnosis; risk for longer hospital stay and being discharged to a care facility were increased in the fully adjusted model. An elevated Mg level of 2.3 mg/dL or higher was a predictor for all adverse outcomes. The magnitude of Mg elevations in patients with levels of 2.3 mg/dL or higher (N=7908) was associated with worse hospital mortality in a dose-response manner. In patients with cardiovascular diseases, Mg levels of 1.5 to 1.69 mg/dL and 2.3 mg/dL or higher both independently predicted poor outcomes including hospital mortality.

Conclusion: Dysmagnesemia in hospitalized patients is common, with hypermagnesemia being most prevalent. Compared with hypomagnesemia, hypermagnesemia is a stronger predictor for poor outcomes. Magnesium supplementation for patients without Mg deficiency should be avoided in the absence of randomized controlled trials documenting a benefit.

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Magnesium (Mg) is one of the dominant intracellular cations. It serves as a catalyst for more than 300 intracellular reactions and has multiple functions in areas of energy production, intracellular calcium regulation, protein synthesis and degradation, and neurotransmitter release.[1] Adequate Mg balance has been reported to reduce the risk of inflammation,[2] diabetes,[3,4] colorectal cancer,[5] stroke,[6] and cardiovascular disease events.[7]

Studies have found that hypomagnesemia in patients with heart failure, critically ill patients, and, recently, patients undergoing dialysis is associated with a high mortality rate.[8] A recent meta-analysis suggested that for every 0.49-mg/dL (0.2-mmol/L) serum Mg reduction, there is a 30% increase in cardiovascular diseases.[9] Hypermagnesemia has traditionally been considered uncommon. In limited studies, it has been associated with elevated mortality, which was attributed to greater neurohormonal activation, parathyroid hormone suppression, and concomitant renal dysfunction and hyperphosphatemia. The extent to which hypermagnesemia is related to clinical outcomes has not been extensively evaluated. Despite lacking outcome information, it has been suggested that increasing Mg intake and mild serum Mg elevation might be beneficial,[3,10-13] based in part on studies reporting a reduced carotid intima-media thickness and soft tissue calcification with Mg supplementation.[14-20]

The aim of the current study was to comprehensively examine the prevalence and clinical

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outcomes of dysmagnesemia in all hospitalized patients in the current era.

PATIENTS AND METHODS

Study Population

The study was approved by the Mayo Clinic Institutional Review Board. All adults (age >18 years) admitted to Mayo Clinic in Rochester, Minnesota, a 2000-bed tertiary medical center, between January 1, 2009, and December 31, 2013, were enrolled. Patients without admission Mg level measurement were excluded. Admission Mg level was defined as serum Mg concentration within 24 hours of admission. For patients with multiple admissions, data from the first admission were used for analysis. A Charlson score[21] was computed for each patient at the time of admission for the comorbidity assessment. Relevant clinical data, including principal admission diagnosis based on the *International Classification of Diseases, Ninth Revision*, codes and patients' disposition, were extracted from the single integrated institutional electronic database (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Patients who were medically stable but were unable to adequately perform daily activities and needed additional care were discharged to an in-hospital rehabilitation unit, a hospital adjacent to the patient's residence ("swing bed"), a skilled nursing facility, or home with home health care assistance on the basis of their performance status.

Statistical Analyses

Continuous variables are reported as mean ± SD for normally distributed data or median (interquartile range) for non–normally distributed data. Categorical variables are reported as number and percentage. Admission Mg levels were categorized on the basis of distribution at the 10th, 25th, 50th, 75th, and 90th percentiles: less than 1.5, 1.5 to 1.69, 1.7 to 1.89, 1.9 to 2.09, 2.1 to 2.29, and 2.3 mg/dL or higher (to convert to mmol/L, multiply by 0.411). Baseline characteristics were compared among groups using analysis of variance for continuous variables and χ^2 test for categorical variables. The percentage of hospital mortality was calculated as the proportion of patients who died in the hospital among the total number of patients. Hospital mortality and Mg were modeled using smoothing splines to allow for nonlinear effects. The restricted cubic spline with 4 knots was used with Mg when fitting the model; plots were constructed using the design library, R version 3.0 (Free Software Foundation).[22] Multivariate logistic regression and linear regression analyses were performed to assess the associations between Mg levels and clinical outcomes including hospital mortality, hospital length of stay (LOS), and discharge disposition. The models were generated sequentially to determine the influence of potential confounders (Supplemental Statistics, available online at http://www.mayoclinicproceedings.org). Odds ratios and 95% CIs were reported. A 2-tailed $P<.05$ was considered significant. Unless specified, JMP statistical software version 9.0 (SAS Institute Inc) was used for analyses.

RESULTS

A total of 288,120 hospital admissions were screened. After excluding patients aged less than 18 years (N=32,139), patients without research authorization (N=1701), patients without Mg measurements (N=151,522), and readmission episodes (N=36,784), 65,974 unique patients were enrolled (Supplemental Figure, available online at http://www.mayoclinicproceedings.org). Among the 151,522 patients without admission Mg measurements, 62,124 (41%) had diseases that were nonmedical and without specific organ dysfunction, including psychiatric and obstetric/gynecologic diseases (Supplemental Results, available online at http://www.mayoclinicproceedings.org).

Baseline Characteristics

The baseline characteristics of the 65,974 participants and groups with various serum Mg levels are summarized in Table 1. The distribution of Mg levels was as follows: less than 1.5 mg/dL, 4957 patients (7.5%); 1.5 to 1.69 mg/dL, 8363 patients (12.7%); 1.7 to 1.89 mg/dL, 14,458 patients (21.9%); 1.9 to 2.09 mg/dL, 17,419 patients (26.4%); 2.1 to 2.29 mg/dL, 12,869 patients (19.5%); and 2.3 mg/dL or higher, 7908 patients (12.0%) (Figure 1, A).

The mean age of the entire cohort was 62±17 years (Table 1). Magnesium levels increased with increasing age from less than 1.5 mg/dL in those 60±17 years to 2.3 mg/dL

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TABLE 1. Baseline Clinical Characteristics of the Study Population[a-c]

Variable	Total patients (N=65,974)	Serum magnesium level at hospital admission (mg/dL)						
		<1.5 (n=4957)	1.5-1.69 (n=8363)	1.7-1.89 (n=14,458)	1.9-2.09 (n=17,419)	2.1-2.29 (n=12,869)	≥2.3 (n=7908)	*P* value
Age (y)	62±17	60±17	61±17	62±17	62±18	63±18	65±17	<.001
Male	35,662 (54.1)	2118 (42.7)	4175 (49.9)	7464 (51.6)	9638 (55.3)	7515 (58.4)	4752 (60.1)	<.001
White	60,711 (92.0)	4532 (91.4)	7682 (91.9)	13,364 (92.4)	16,068 (92.2)	11,895 (92.4)	7170 (90.7)	<.001
Charlson score	2.1±2.5	2.6±2.8	2.3±2.6	2.0±2.5	1.9±2.4	1.9±2.4	2.2±2.5	<.001
eGFR (mL/min/1.73 m^2)	75±31	75±33	77±30	79±29	78±29	74±29	61±34	<.001
Alcohol dependence	3723 (5.6)	354 (7.1)	486 (5.8)	798 (5.5)	944 (5.4)	674 (5.2)	467 (5.9)	<.001
Diabetes mellitus	14,207 (21.5)	1361 (27.5)	2098 (25.1)	3083 (21.3)	3407 (19.6)	2448 (19.0)	1810 (22.9)	<.001
Principal diagnosis								<.001
Cardiovascular	16,647 (25.2)	569 (11.5)	1366 (16.3)	2984 (20.6)	4758 (27.3)	4278 (33.2)	2682 (33.9)	
Hematologic/oncological	11,782 (17.9)	1575 (31.8)	2302 (27.5)	3081 (21.3)	2578 (14.8)	1472 (11.4)	774 (9.8)	
Infectious	2482 (3.8)	341 (6.9)	378 (4.5)	508 (3.5)	581 (3.3)	367 (2.9)	307 (3.9)	
Endocrine/metabolic	2479 (3.8)	203 (4.1)	284 (3.4)	583 (4.0)	634 (3.6)	451 (3.5)	324 (4.1)	
Respiratory	3060 (4.6)	142 (2.9)	328 (3.9)	600 (4.2)	804 (4.6)	707 (5.5)	479 (6.1)	
Gastrointestinal	7943 (12.0)	624 (12.6)	1104 (13.2)	1984 (13.7)	2167 (12.4)	1251 (9.7)	813 (10.3)	
Injury/poisoning	9321 (14.1)	690 (13.9)	1150 (13.8)	2078 (14.4)	2668 (15.3)	1821 (14.2)	914 (11.6)	
Other	12,260 (18.5)	813 (16.4)	1451 (17.4)	2640 (18.2)	3229 (18.5)	2522 (19.6)	1605 (20.3)	
Magnesium supplement before admission	7222 (11.0)	723 (14.6)	1014 (12.1)	1531 (10.6)	1770 (10.2)	1342 (10.4)	842 (10.6)	<.001
Potassium at admission (mEq/L)	4.2±0.6	4.0±0.7	4.1±0.6	4.2±0.6	4.2±0.6	4.3±0.6	4.4±0.8	<.001
Albumin at admission (g/dL) (n=14,075)	3.49±0.68	3.35±0.73	3.4±0.71	3.43±0.69	3.49±0.66	3.58±0.66	3.54±0.67	<.001
Ionized calcium (mg/dL) (n=33,255)	4.76±0.40	4.6±0.50	4.69±0.39	4.76±0.38	4.8±0.35	4.83±0.37	4.81±0.43	<.001
Phosphorus (mg/dL) (n=42,336)	3.78±1.10	3.7±1.11	3.7±1.02	3.66±0.97	3.7±0.94	3.8±1.06	4.29±1.58	<.001

[a]eGFR = estimated glomerular filtration rate.

[b]Continuous data are presented as mean ± SD; categorical data are presented as No. (percentage).

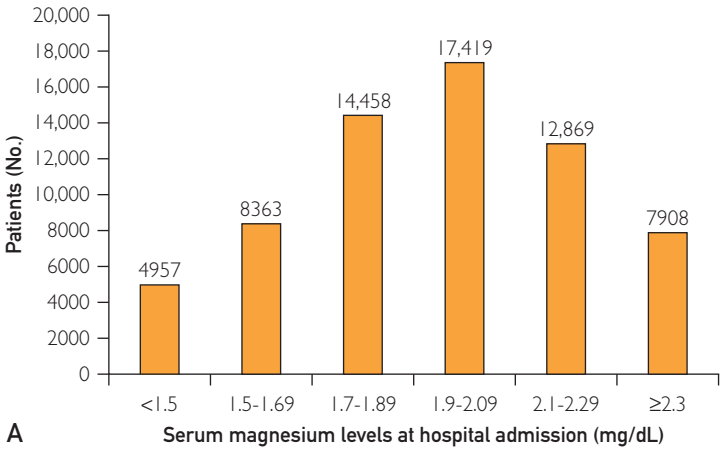
[c]SI conversion factors: To convert magnesium values to mmol/L, multiply by 0.411; to convert potassium values to mmol/L, multiply by 1.0; to convert albumin values to g/L, multiply by 10; to convert ionized calcium values to mmol/L, multiply by 0.25; to convert phosphorus values to mmol/L, multiply by 0.323.

or higher in those 65±17 years. The percentage of men increased from 42.7% (2118 of 4957 patients) in those with Mg levels less than 1.5 mg/dL to 60.1% (4752 of 7908 patients) in those with Mg levels of 2.3 mg/dL or higher. The Charlson comorbidity scores revealed a U-shaped distribution, with the best scores at Mg levels of 1.9 to 2.29 mg/dL. Estimated glomerular filtration rate (eGFR) had a similar distribution pattern, with the best eGFR in Mg levels of 1.7 to 1.89 mg/dL.

Lower Mg values were associated with a principal diagnosis of hematologic/oncological diseases, consistent with findings in previous studies.[12,23,24] Higher Mg values were associated with cardiovascular diseases (Table 1). Diseases of the respiratory system increased from 2.9% (142 of 4957 patients) in patients with an Mg level of less than 1.5 mg/dL to 6.1% (479 of 7908) in those with an Mg level of 2.3 mg/dL or higher (Figure 1, B). The biochemical data that can affect or be affected by Mg were also examined. With increasing Mg level, serum potassium, albumin, ionized calcium, and phosphorus levels increased slightly but significantly, from 4.0±0.7 to 4.4±0.8 mEq/L, 3.35±0.73 to 3.54±0.67 g/dL, 4.6±0.50 to 4.81±0.43 mg/dL, and 3.7±1.11 to 4.29±1.58 mg/dL, respectively (all $P<.001$).

Clinical Outcomes

For overall hospital mortality, assessed by restricted cubic spline, the lowest mortality risk was in patients with serum Mg levels within 1.7 to 1.89 mg/dL (Figure 2, A). The percentage of hospital mortality also revealed that the absolute mortality increased substantially with worse dysmagnesemia (Figure 2, B).



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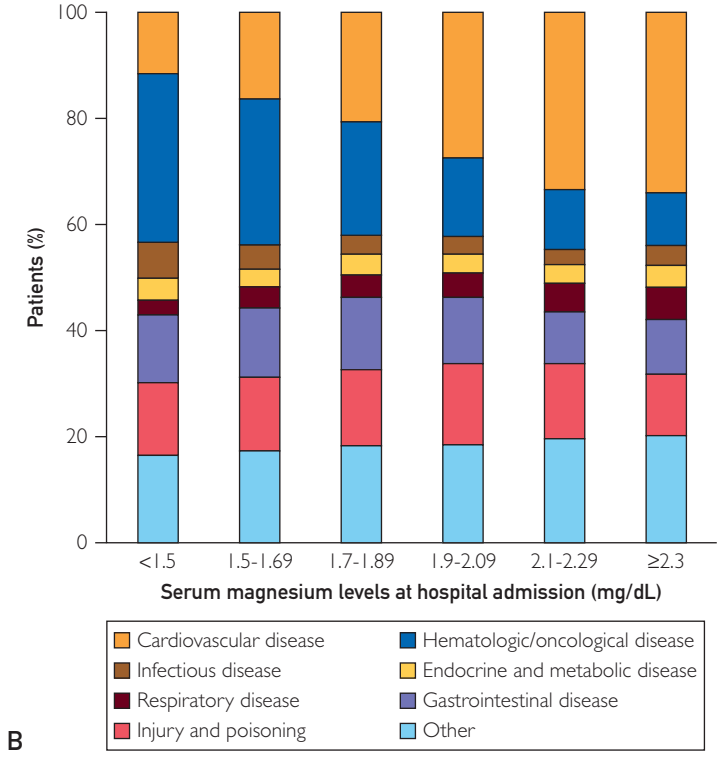

B

FIGURE 1. A, Distribution of serum magnesium levels among the 65,974 study patients at hospital admission. B, Percentage distribution of principal diagnoses in patients with various admission magnesium levels. SI conversion factor: To convert magnesium values to mmol/L, multiply by 0.411.

Logistic regression was used to determine whether Mg alterations contributed to hospital mortality and patient disposition. Linear regression was used to determine hospital LOS. Magnesium levels of less than 1.7 mg/dL and 2.1 mg/dL or higher were both associated with increased hospital mortality in an unadjusted model (model 1) (Table 2). When the model was adjusted for age, sex, eGFR, and Charlson score (model 2), Mg levels of less than 1.7 mg/dL and 2.3 mg/dL or higher continued to be associated with increased mortality. When the model was fully adjusted (model 3), including all elements in model 2 and principal diagnosis, only Mg levels of 2.3 mg/dL or higher were associated with increased hospital mortality (Figure 3, A). Longer hospital stay was also associated with Mg levels of less than 1.7 mg/dL and 2.3 mg/dL or higher (Table 2), as was increased discharge to a care facility in hospital survivors (n=64,473), an important predictor of long-term survival[25] (Table 2).

Subgroup analysis was performed for patients with hypermagnesemia (Mg level ≥2.3 mg/dL [n=7908]). We found that more patients with Mg levels of 2.9 mg/dL or higher were taking oral Mg (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). In the fully adjusted model (model 4, which included hyperphosphatemia [implicated in mortality[26-28]]), the risk for hospital mortality and being discharged to a care facility was increased when Mg levels were 2.3 mg/dL or higher. The mortality risk increased progressively with increasing Mg level (Figure 3, B). Hospital LOS was increased with Mg levels of 2.5 mg/dL or higher in the fully adjusted model (model 4) (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org).

Because patients admitted for cardiovascular diseases constituted the largest group (n=16,647), 25.2% of the entire cohort, subgroup analysis of clinical outcomes was undertaken. The lowest hospital mortality was observed in patients whose Mg levels were within 1.9 to 2.09 mg/dL. In the fully adjusted logistic regression model (model 2), Mg levels of 1.5 to 1.69 mg/dL and 2.3 mg/dL or higher were associated with increased hospital mortality. Magnesium levels of less than 1.7 mg/dL and 2.3 mg/dL or higher were associated with increased hospital LOS in the fully adjusted linear regression model (model 2) (Supplemental Table 4, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

In this study, we found a frequent occurrence of dysmagnesemia in a large, mixed population of

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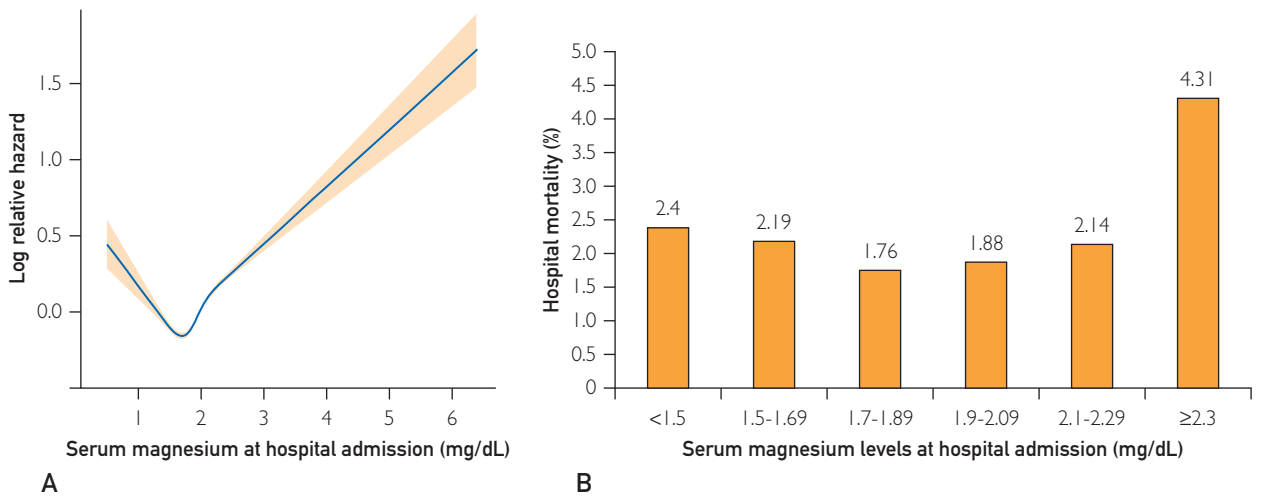

FIGURE 2. A, Hospital mortality rates analyzed with restricted cubic spline, using the admission magnesium level as a function of mortality. B, Hospital mortality rates in percentage, showing elevated mortality rates in patients with hypomagnesemia and hypermagnesemia ($P<.05$). SI conversion factor: To convert magnesium values to mmol/L, multiply by 0.411.

hospitalized patients in which only 21.9% (14,458 of 65,974 patients) had an optimal Mg level (1.7-1.89 mg/dL). Patients with dysmagnesemia had worse clinical outcomes, including hospital mortality, LOS, and discharge to a care facility.

Previous studies have found that hypomagnesemia occurs in approximately 10% of hospitalized patients, most commonly in critically ill patients, those with heart failure, and patients with concurrent electrolyte abnormalities.[8] Hypermagnesemia has been considered uncommon.[29] In the current study, we found that the occurrence of elevated Mg level of 2.1 mg/dL or higher was more than 1.5-fold that of Mg levels lower than 1.7 mg/dL, a distribution pattern of Mg alterations differing from those in previous studies.

Several factors could have contributed to the change in distribution. First, most studies of the prevalence of dysmagnesemia, with the exception of a recent study of Mg in patients undergoing dialysis,[12] were conducted using data that were more than 10 years old. The current study encompasses recent data (2009-2013) over a relatively short study period during which no major changes in practice (relevant to Mg) are likely to have occurred. It is, therefore, more reflective of recent practice. Second, detrimental effects of hypomagnesemia have been much more appreciated, which could have translated to more aggressive Mg use. For instance, patients with cardiovascular disease in this study had a higher rate of hypermagnesemia than patients hospitalized for other disorders, differing from previous reports.[30,31] This finding could be linked to the awareness of the detrimental effects of hypomagnesemia and risk for cardiac arrhythmia, congestive heart failure, and other cardiovascular complications.[32,33] Respiratory diseases in this study were also associated with hypermagnesemia, which was unexpected[34] although not entirely surprising. This result could potentially be related to reports of Mg-mediated airway relaxation and Mg-mediated immunomodulation and anti-inflammatory effects.[35-37] Magnesium as an adjunctive therapy has been advocated for patients with moderate to severe airway diseases such as asthma and chronic obstructive pulmonary disease,[38-40] despite inconclusive evidence of its benefit.[40,41] Third, because the number of patients with chronic kidney disease (CKD) has steadily increased, more patients might have development of hypermagnesemia due to their CKD. Parallel to eGFR reduction, however, renal Mg absorption is also reduced,[42] and hypermagnesemia thus might not develop until eGFR declines to less than 30 mL/min/1.73 m^2. In our patients with hypermagnesemia, the eGFR was higher than 40 mL/min/1.73 m^2.

TABLE 2. Clinical Outcomes in the 65,974 Study Patients[a-c]

Outcome	Serum magnesium level at hospital admission (mg/dL)					
	<1.5 (n=4957)	1.5-1.69 (n=8363)	1.7-1.89 (n=14,458)	1.9-2.09 (n=17,419)	2.1-2.29 (n=12,869)	≥2.3 (n=7908)
Hospital mortality						
Deaths	119 (2.4)	183 (2.2)	255 (1.8)	327 (1.9)	276 (2.1)	341 (4.3)
Mortality OR (95% CI)						
Model 1: unadjusted	1.37 (1.10-1.70)	1.24 (1.03-1.51)	1 (reference)	1.07 (0.90-1.26)	1.22 (1.03-1.45)	2.51 (2.13-2.96)
Model 2: adjusted for age, sex, eGFR, and Charlson score	1.29 (1.03-1.61)	1.21 (1.01-1.47)	1 (reference)	1.06 (0.90-1.25)	1.13 (0.95-1.34)	1.88 (1.59-2.23)
Model 3: Model 2 and principal diagnosis	1.19 (0.95-1.49)	1.16 (0.96-1.42)	1 (reference)	1.03 (0.87-1.22)	1.12 (0.94-1.33)	1.86 (1.56-2.21)
Length of hospital stay (d)						
Median (IQR)	6 (4-9)	5 (3-8)	4 (2-7)	4 (2-6)	4 (2-7)	4 (2-8)
Relative prolongation (95% CI)						
Model 1: unadjusted	1.44 (1.40-1.48)	1.19 (1.16-1.22)	1 (reference)	0.93 (0.91-0.94)	0.96 (0.94-0.98)	1.11 (1.08-1.13)
Model 2: adjusted for age, sex, eGFR, and Charlson score	1.43 (1.39-1.47)	1.19 (1.16-1.22)	1 (reference)	0.93 (0.91-0.94)	0.95 (0.93-0.97)	1.07 (1.05-1.10)
Model 3: Model 2 and principal diagnosis	1.38 (1.35-1.42)	1.17 (1.14-1.20)	1 (reference)	0.94 (0.92-0.96)	0.98 (0.96-0.99)	1.11 (1.08-1.13)
Discharge disposition						
Hospital survivors (n=64,473)	4838	8180	14,203	17,092	12,593	7567
Discharge type/location[d]						
Home	3477 (71.9)	6167 (75.4)	11,003 (77.5)	13,380 (78.3)	9659 (76.7)	5387 (71.2)
Home health care	541 (11.2)	680 (8.3)	937 (6.6)	1106 (6.5)	827 (6.6)	628 (8.3)
Hospital rehabilitation	98 (2.0)	155 (1.9)	248 (1.8)	328 (1.9)	232 (1.8)	151 (2.0)
Skilled nursing facility	703 (14.5)	1126 (13.8)	1941 (13.7)	2154 (12.6)	1767 (14.0)	1322 (17.5)
Swing bed	19 (0.4)	52 (0.6)	74 (0.5)	124 (0.7)	108 (0.9)	79 (1.0)
Discharge to a care facility, OR (95% CI)						
Model 1: unadjusted	1.08 (0.99-1.17)	1.03 (0.95-1.11)	1 (reference)	0.95 (0.89-1.01)	1.06 (0.99-1.13)	1.36 (1.27-1.46)
Model 2: adjusted for age, sex, eGFR, and Charlson score	1.17 (1.07-1.29)	1.07 (0.99-1.16)	1 (reference)	0.94 (0.88-1.00)	1.02 (0.95-1.09)	1.25 (1.16-1.35)
Model 3: Model 2 and principal diagnosis	1.21 (1.10-1.33)	1.09 (1.01-1.18)	1 (reference)	0.91 (0.85-0.97)	0.99 (0.93-1.06)	1.26 (1.16-1.36)

[a]eGFR = estimated glomerular filtration rate; IQR = interquartile range; OR = odds ratio.
[b]Data are presented as No. (percentage) unless indicated otherwise.
[c]SI conversion factor: To convert magnesium values to mmol/L, multiply by 0.411.
[d]Percentages are based on number of survivors.

Thus, additional Mg intake could have contributed to the hypermagnesemia. Indeed, a higher percentage of patients with hypermagnesemia were taking Mg-containing preparations.

To analyze mortality risk among patients with various Mg levels, a serum Mg level within 1.7 to 1.89 mg/dL was used as a reference because that range was associated with the lowest hospital mortality and any deviation resulted in a sharp increase in mortality risk (Figure 2, A). Additionally, we used only the admission serum Mg level for analysis. Serum Mg, when in equilibrium, is a reasonable indication of the patient's Mg status and has been reported to correlate best with Mg concentration in the bone.[43,44] We avoided using subsequent Mg measurements during the hospital stay because patients might receive treatment to normalize Mg level but they can still be Mg deficient.[45]

Reduced survival was noted in patients with both low and high Mg levels. The highest Mg range (≥2.3 mg/dL), however, was the strongest independent predictor of hospital mortality, a 1.9-fold risk elevation compared with that in patients with normomagnesemia. Consistently, subgroup analysis revealed that elevated Mg levels had a dose-response relationship with mortality risk.

The underlying mechanism(s) involved in the development of poor clinical outcomes in patients with dysmagnesemia are not fully understood. In addition to its known critical regulatory role in numerous intracellular reactions,[46] in recent years Mg has been found to regulate intracellular calcium movements via interaction with

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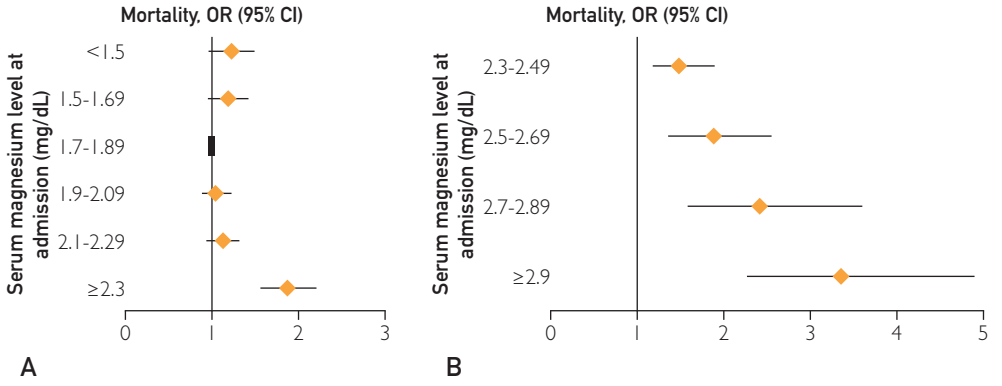

FIGURE 3. A, Odds ratios (ORs) for hospital mortality in patients with various admission magnesium levels, adjusted for age, sex, estimated glomerular filtration rate, Charlson score, and principal diagnosis. B, Odds ratios for hospital mortality in patients with hypermagnesemia at hospital admission, adjusted for age, sex, estimated glomerular filtration rate, Charlson score, principal diagnosis, and serum phosphorus level. SI conversion factor: To convert magnesium values to mmol/L, multiply by 0.411.

ryanodine receptor (RyR) channels (RyR forms the calcium release channels in the sarcoplasmic reticulum) in cardiac myocytes. Magnesium inhibits RyR-mediated sarcoplasmic reticulum calcium release by competing with calcium for activation sites, as well as by binding to low-affinity, nonselective divalent cation inhibition sites.[47-49] Presumably through calcium dysregulation, hypomagnesemia predisposes patients to arrhythmia and sudden death, while hypermagnesemia may cause weakening of cardiac contraction. In the current study, when we adjusted the admission diagnosis, hypomagnesemia was no longer a predictor of mortality, suggesting a disease-specific effect of hypomagnesemia. Indeed, further subgroup analysis of patients with cardiovascular disease revealed an elevated risk of hospital mortality in cardiac patients with hypomagnesemia (magnesium levels <1.7 mg/dL), consistent with findings in previous reports.[30,50] Magnesium elevation, on the contrary, elevated risk of hospital mortality and other poor outcomes across all admission diagnoses. In vessels, Mg produces vasodilation through competing with the vascular smooth muscle cells for calcium uptake and likely involves other mechanisms.[51] Magnesium also increases prostaglandin binding and induces endothelial-dependent vasodilation, reducing blood pressure.[32,33,52] Additionally, Mg exerts anti-inflammatory, immunomodulatory,[53,54] and anticalcification effects.[18-20] Hypomagnesemia can thus result in vascular and soft tissue calcification, while hypermagnesemia can also increase the risk of soft tissue calcification via parathyroid hormone inhibition and less bone turnover, especially in patients with CKD.[55]

Our study has several clinical implications. We found that a large fraction of admitted patients did not have Mg measurements. Among these, 59% (89,398 of 151,522 patients) had medical conditions suggesting a degree of underrecognition of the possibility of Mg alteration. The higher rate of hypermagnesemia could have been related to an increased Mg use in practice. Such clinical decisions might be influenced by publications reporting that Mg intake is correlated with beneficial effects including reductions in serum lipids, hyperglycemia, metabolic syndrome, obesity, insulin resistance, and diabetes mellitus[56,57] and when given in conjunction with taurine or potassium, lowers blood pressure, retards atherogenesis, prevents arrhythmias, and stabilizes platelets,[32,33,58-60] although these findings have not been confirmed. Magnesium intake has also been reported in some, but not all, studies[56,57,61-64] to correlate with lower occurrence of cerebrovascular accidents, cardiovascular disease, arrhythmias, and left ventricular hypertrophy. These reports, coupled with the paucity of hard data on the consequences of hypermagnesemia itself, have even led to recommendations of

daily Mg supplementation, regardless of Mg status.[60] Given the high occurrence rate, poor outcomes of dysmagnesemia, and low cost of Mg measurement, admission serum Mg measurement should be considered. Moreover, the results of this study sound a note of warning against indiscriminate Mg use.

This study has several limitations. First, it is a retrospective observational study. Second, we were unable to document the specific clinical manifestations of dysmagnesemia and specific cause of death because the data were generated from our electronic database. These data, however, were not the focus of the study. Third, albumin binds approximately 15% to 20% of circulating Mg.[65] Alterations in serum albumin concentration could alter the serum Mg value, especially given that the albumin levels in our patients were slightly, but significantly, higher in those with hypermagnesemia ($P<.001$). However, the magnitude of the albumin increase was small (about 0.07 g/L) and thus unlikely to have dramatically altered the Mg value. Fourth, the patient population was relatively homogeneous, predominantly white. A heterogeneous population would have been desirable to ascertain the clinical effects of dysmagnesemia across a broader patient population. Fifth, we used serum Mg level instead of the more precise methods of Mg tolerance tests and Mg loading tests.[66-68] These measuring methods are time consuming and impractical in the setting of hospital admission. Serum Mg measurement is a well-established measurement technique. Most published studies use serum Mg, making it easier to compare the results of the current study with the existing literature. Lastly, we could not completely rule out the possibility that some features in the lives of the study patients might have gone hand in hand with the development of Mg alterations, such as diseases necessitating diuretic use that might have been contributory to poor outcomes. However, we fully adjusted all identifiable factors. Although we can only establish an association of Mg alterations and poor clinical outcomes, the strength of the association was enhanced given the large number of patients, pronounced differences, and cause-response relationships consistently observed in the study.

CONCLUSION

Dysmagnesemia is common at hospital admission. It appears that Mg alterations, especially hypermagnesemia, afford the most probable independent influence on worse patient outcomes. Magnesium measurement for admitted patients, especially patients admitted to medical units, should be encouraged. Caution should be advised before advocating Mg supplementation for patients without Mg deficiency.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CKD** = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **LOS** = length of stay; **Mg** = magnesium; **RyR** = ryanodine receptor

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