

Active Supplementation With Magnesium Sulfate May Be Associated With Worse Prognosis in Sepsis: A Retrospective Analysis of The MIMIC-IV Database

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Research

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Abstract

Background: Magnesium plays pivotal roles in physiological processes. Previous studies have shown that magnesium acts as an important mediator in ameliorating cellular injury and preventing the release of proinflammatory cytokines in septic patients. Therefore, we speculated that the serum magnesium ion level may affect the outcome of sepsis. However, research in this area is rarely reported and it is worth exploring.

Methods: We conducted a retrospective study based on the MIMIC-IV database. According to the time-weighted magnesium levels during the ICU stay, we analyzed the relationship between serum magnesium levels and 28-day mortality and 90-day mortality using a time-dependent Cox proportional hazard model and restricted cubic splines. Additionally, we examined the effect of magnesium sulfate supplementation on prognosis with a time-fixed and time-dependent Cox model and restricted cubic splines.

Results: In total, 8175 patients were included in this study. Patients with hypo-, normo- and hypermagnesemia were 22.87%, 66.84%, and 10.29%, respectively. When adjusted for confounders, hypermagnesemia was significantly associated with both 28-day mortality (HR=1.42, 95% CI=1.23-1.64, $p<0.001$) and 90-day mortality (HR=1.42, 95% CI=1.24-1.64, $p<0.001$). However, no significant difference was found between hypomagnesemia and mortality of septic patients (28-day mortality: HR=1.09, 95% CI=0.86-1.37, $p=0.486$, 90-day mortality: HR=1.06, 95% CI=0.85-1.34, $p=0.573$). For those who received magnesium sulfate supplementation, there was no significant difference among hypo-, normo-, and hypermagnesemia before MgSO₄ supplementation. Interestingly, subsequent hypermagnesemia (28-day mortality: HR=1.44, 95% CI=1.17-1.78, $p=0.001$, 90-day mortality: HR=1.43, 95% CI=1.16-1.77, $p=0.001$), and even still hypomagnesemia (28-day mortality: HR=1.51, 95% CI=1.15-1.99, $p=0.003$, 90-day mortality: HR=1.53, 95% CI=1.18-1.99, $p=0.001$) after MgSO₄ supplement were significantly associated with increased 28-day and 90-day mortality after adjustment for confounders.

Conclusion: Hypermagnesemia was significantly associated with higher risk of 28-day mortality and 90-day mortality. Active supplementation with magnesium sulfate may be associated with a worse prognosis in sepsis.

Introduction

Magnesium (Mg), as the fourth most abundant electrolyte in the body, plays pivotal roles in physiological processes[1-4]. Mg may exert immunological, respiratory, and cardiovascular effects through energy storage and transfer, protein and enzyme synthesis, inflammation and homeostasis[1-3]. Typically, the normal range of Mg is 1.7-2.4 mg/dl (0.66-1.05 mmol/L), hypomagnesemia was defined as serum Mg level less than 1.7 mg/dl, and hypermagnesemia was described as a serum Mg level higher than 2.4 mg/dl[5]. Mg is absorbed in the small intestine and excreted primarily in the kidneys[5]. Mg disorders, including hypomagnesemia and hypermagnesemia, are common electrolyte abnormalities in critically ill patients due to their high severity of illness and the complex therapies provided[6, 7]. A recent

retrospective cohort study revealed that the prevalence of hypomagnesemia was 23.8% and that the incidence of hypermagnesemia was 11.9% among adult patients admitted to the intensive care unit[7]. Reports have shown that hypomagnesemia and hypermagnesemia could lead to important clinical symptoms and consequences, such as cardiac arrhythmias and neurotoxicity[8]. Several studies have shown that serum Mg levels are an independent risk factor for death and hypomagnesemia or hypermagnesemia have been associated with increased mortality rates in critically ill patients[9-12]. This understanding is particularly important in patients who develop sepsis, triggered by a dysregulated host response to infection with high mortality[13, 14]. These patients are more likely to have Mg abnormalities[11, 15]. There are various reasons why septic patients may acquire abnormal serum Mg levels, such as inadequate intake of Mg, oversupplementation with magnesium sulfate (MgSO₄), drugs, such as proton pump inhibitors and diuretics, or kidney dysfunction[6]. Interestingly, some studies have demonstrated that Mg is an important mediator that ameliorates cellular injury and prevents the release of proinflammatory cytokines during the development of sepsis[3, 16]. However, the impact of abnormal Mg levels on patients with sepsis is rarely reported and the specific association between serum Mg and mortality of septic patients is still not clear. In addition, to the best of our knowledge, the influence of magnesium sulfate supplementation on the risk of mortality in septic patients has not been studied before. Therefore, we conducted a retrospective clinical trial using the MIMIC-IV database in light of both time-fixed and time-varying models to explore the impact of serum Mg concentration on clinical outcomes (mainly 28-day and 90-day mortality), and further evaluate the potential association between magnesium sulfate supplementation and the mortality rate of septic patients.

Materials And Methods

Data extraction

This retrospective study extracted data from the Multiparameter Intelligent Monitoring in Intensive Care Database IV (MIMIC IV), which contains ICU patient data ranging from 2008 to 2019. This database was approved by the Institutional Review Boards (IRB) of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BDMC). One of the authors (Shiyu Zhou) obtained access to reach and extract the data (certification No. 35931520)

Inclusion and Exclusion criteria

Adult patients diagnosed with sepsis within 24 hours after ICU admission were eligible for inclusion into the study. The exclusion criteria were patients without any hospitalization records, patients who lacked Mg measurement during the whole ICU stay, and patients less than 16 years old.

Sepsis definition

Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (sepsis 3.0). Infectious patients with a SOFA score of 2 points or more were diagnosed with sepsis[14].

Endpoints

The primary endpoints of the study were 28-day mortality and 90-day mortality rates, and the secondary endpoint was whether supplementation with magnesium sulfate was beneficial or harmful.

Statistical analysis

Continuous variables are reported as medians (interquartile ranges [IQRs]) and were compared using ANOVA, while categorical variables are presented as counts with percentages and were compared with the chi-square test.

The risks of 28- and 90-day mortality were estimated by time-dependent Cox proportional hazard model based on continuous and categorical Mg levels. In our primary analysis, Mg levels were treated as the time-varying variable and divided into three levels (hypomagnesemia <1.7 mg/dl, normomagnesemia 1.7-2.4 mg/dl, and hypermagnesemia >2.4 mg/dl). We used the time-dependent Cox model to examine the nonlinear relationship between mortality and Mg levels as the continuous time-varying variable with restricted cubic splines (4 knots). In the spline model, the lower range of normal Mg levels (1.7 mg/dl) was set to the reference (HR=1). Three models were used for confounder correction: Model 1 was unadjusted; Model 2 was adjusted for baseline demographic characteristics, including age, gender, admission type, ethnicity, marital status, and insurance; and Model 3 was further adjusted for mean arterial pressure (MAP), weight, MgSO₄ supplement, ventilator(VENT), continuous renal replacement treatment (CRRT), use of vasopressor (VASO), AKI, hemoglobin, potassium, platelets, white blood cells(WBCs), chloride, lactate, sodium, creatinine, bicarbonate, heart rate, respiratory rate, temperature, saturation of peripheral oxygen(SpO₂), urea nitrogen (BUN), and infection site.

Additionally, to examine the associations of 28- and 90-day mortality with Mg levels pre- and post-MgSO₄ supplementation, we further performed a time-fixed and time-dependent Cox model as well as restricted cubic splines. Pre-MgSO₄ Mg levels were defined as the baseline Mg before MgSO₄ supplementation and analyzed as the time-fixed variable. The subsequent Mg levels post-MgSO₄ were treated as the time-varying variable.

Results

Study cohort

In total, 8175 patients were included in this study (Figure 1). Patients with hypo-, normo- and hypermagnesemia were 22.87%, 66.84%, and 10.29%, respectively. Patients were 67.51 years old on average, and 63.73% were male. The average SAPS-II and SOFA scores were 34.23 and 4.57, respectively. A total of 8175 patients were included in our study, among them, 1870(22.87%), 5464(66.84%), and 841(10.29%) patients had hypo-, normo-, and hypermagnesemia, respectively (Table 1). The mean baseline Mg level was 1.95 mmol/L. Characteristics such as age, respiratory rate, heart rate, temperature, MAP, weight, lactate level, SpO₂, WBC, platelets, creatinine, hemoglobin, calcium, potassium, BUN,

bicarbonate, daily urine output, baseline Mg level and SAPS-II, SOFA, Charlson comorbidity index (CCI) and GCS scores, infection site, VENT, VASO, CRRT, and incidence of AKI were found to be significantly different between survivors and nonsurvivors (Table 1).

Association of Mg levels with 28- and 90-day mortality

Compared to normomagnesemia, there was a significant association of hypermagnesemia with 28- and 90-day mortality (HR=1.68, 95% CI=1.47-1.91; HR=1.64, 95% CI=1.44-1.87) but hypomagnesemia showed no statistical significance ($p>0.916$) when compared with normomagnesemia in the unadjusted model (Table 2). In full correction (Table 2 Model 3), the hazard ratio (HR) of hypermagnesemia decreased to 1.42 (95% CI=1.23-1.64) and 1.42 (95% CI=1.24-1.64) at 28 and 90 days, respectively. The results of the spline model (Figure 2) based on the continuous variable were consistent with the results of the categorical variable (Table 2). Higher Mg levels were associated with an increased risk of 28- and 90-day mortality in all correction models. However, there was no significant association between lower Mg levels and mortality (Figure 2).

For further confirmation of our results, we developed sensitivity analyses from different points and obtained similar results (Supplement Table).

The association between mortality and Mg levels pre- and post-MgSO₄ supplementation

Mg levels of the pre-MgSO₄ supplement were not associated with mortality at 28- and 90 days after adjustment for confounders (Table 3). However, in patients receiving MgSO₄ supplement, an increased risk of 28-day mortality was found in hypermagnesemia compared to normomagnesemia (HR=1.69, 95% CI=1.40-2.03). When further adjusted for the baseline characteristics (Table 3 Model 3), subsequent hypermagnesemia (HR=1.44, 95% CI=1.17-1.78, $p=0.001$) and even still hypomagnesemia (HR=1.51, 95% CI=1.15-1.99, $p=0.003$) after MgSO₄ supplementation were significantly associated with increased 28-day mortality after adjustment for confounders. The association among 90-day mortality showed similar results.

In the spline model regarding pre-MgSO₄ supplementation, there was no significant association between mortality and Mg levels (Figure 3 A and D). The mortality in hypermagnesemia seemed higher than that in patients in the normal range, but the difference was not statistically significant. After correction, the reference line was included in the 95% CI of HRs for any Mg concentrations, which indicated no significant association between baseline Mg and 28- and 90-day mortality (Figure 3 B-C E-F). However, there was a sharp U-shaped relationship between Mg levels and 28- and 90-day mortality post-MgSO₄ supplementation (Figure 4). Unlike the results in the total population (Table 2), after receiving MgSO₄ supplementation, patients with subsequently higher and lower Mg levels had a steeply increased risk of 28- and 90-day mortality, and this association remained after adjusting for confounders. More importantly, the risk of mortality caused by subsequent lower Mg after MgSO₄ seemed deadier than those in higher Mg after correction (Model 3 in Table 3 and Figure 4 C and F).

Discussion

In this retrospective study, a total of 8175 patients were analyzed, and the proportions of patients with hypo-, normo-, and hypermagnesemia were 22.87%, 66.84%, and 10.29%, respectively. Of note, hypermagnesemia was significantly associated with both 28-day and 90-day mortality of septic patients when adjusted for cofounders. Unexpectedly, septic patients with subsequent hyper- and even still hypomagnesemia who received MgSO_4 supplementation were found to have a significantly increased risk of 28-day and 90-day mortality.

Mg, the so-called “the forgotten electrolyte”, is an essential element of life support[17, 18]. Magnesium disorders are commonly reported in critically ill patients and a great number of patients are characterized by hypomagnesemia, with a range of 22% and 60%[3]. Our study confirmed that the morbidity of hypomagnesemia is as high as 22.87%, which was consistent with a previous report[19]. Interestingly, the incidence of hypermagnesemia was almost one-half that of hypomagnesemia in septic patients. Perhaps due to the low incidence of hypermagnesemia in the past, we ignored this type of electrolyte disorder. There is no magnesium regulatory system other than urinary excretion, and Mg levels rise as kidney function declines[20]. Unfortunately, more than 50% of the causes of acute kidney injury (AKI) are sepsis [21], and AKI may result in hypermagnesemia in septic patients. Due to the development and popularity of CRRT, hypermagnesemia was less frequent than hypomagnesemia.

Notably, both hypomagnesemia and hypermagnesemia are associated with disease severity and various clinical symptoms, including cardiac arrhythmias, neurotoxicity, diminished deep tendon reflexes, muscle weakness and even cardiac arrest[3]. Several studies revealed that hypomagnesemia was associated with increased mortality and poor prognosis in critically ill patients with a higher prevalence of severe sepsis and septic shock[11, 15]. For example, a prospective observational study showed that patients who developed hypomagnesemia had significantly longer ICU stays and higher mortality[11]. Limaye et al[15] demonstrated that patients with hypomagnesemia needed longer mechanical ventilation support and had higher mortality than those with normal Mg levels. Similarly, two studies[22, 23] on a relatively large number of patients also concluded that hypomagnesemia was associated with higher mortality. Studies have shown that hypomagnesemia increases the mortality of patients, and a small number of studies have also found that hypermagnesemia can increase the mortality of patients. In a cross-sectional study by Haider et al[24], the authors analyzed baseline Mg concentrations of over 5000 patients and showed that hypermagnesemia was a strong independent risk factor for mortality in a multivariate Cox regression model. Our study evaluated the time-weighted Mg value because this would reflect the total Mg exposure during their ICU stay, which we believe would be more representative to reveal the association between Mg and mortality. Unexpectedly, hypermagnesemia was significantly associated with increased 28-day and 90-day mortality. In addition, to explore the nonlinear relationship between Mg and our primary endpoints, we used restricted cubic splines based on a time-dependent model, and the results of the spline model were the same as those of the Cox model. For further confirmation of our results, we developed sensitivity analyses from different views and obtained similar results.

Therefore, combined with our study, hypomagnesemia was not associated with mortality while hypermagnesemia was harmful to septic patients. The reasons may be as follows. At the acute phase of sepsis, the acquired causes of hypomagnesemia can be attributed to decreased oral intake or gastrointestinal absorption, or redistribution triggered by severe illness, or liquid dilution during fluid resuscitation[25, 26]. We may speculate that low levels of serum Mg could be relatively transient and be adjusted or even reversed with the onset of AKI or subsequent supplementation with magnesium sulfate. Previous studies[3, 11, 27] mainly focused on baseline Mg concentrations at admission, which would not reflect the whole level of Mg, thus ignoring some potential risk factors during the development of sepsis that could influence the mortality rate. Hypermagnesemia might cause severely lowered blood pressure, bradycardia, respiratory paralysis, coma, and cardiac arrest, which might aggressively deteriorate sepsis development[28]. The excretion of Mg is controlled primarily by the kidney[29], which is one of the most vulnerable organs during the development of sepsis[30]. Hypermagnesemia may be associated with acute kidney injury[31] and thus cause poor prognosis in septic patients. Since the impact of hypermagnesemia in septic patients has been studied less than hypomagnesemia, the specific mechanism of hypermagnesemia on body function remains unclear.

Since the treatment of hypomagnesemia remains unclear, we further explored the effects of Mg supplements (magnesium sulfate, $MgSO_4$) on the relationship between serum Mg levels and mortality. Considering the different timings of Mg supplementation in different patients, we assessed Mg levels in a time-fixed and time-varying manner. A time-fixed manner regarded baseline Mg levels before receiving magnesium sulfate and a time-varying manner was presented as the Mg levels after magnesium sulfate supplementation. Interestingly, in our present study, Mg levels of the pre- $MgSO_4$ supplement were not associated with mortality when adjusted for confounders, however, after the administration of the $MgSO_4$ supplement, the subsequent hyper- and hypomagnesemia were associated with increased 28-day and 90-day mortality. The further spline model showed similar results. This result indicated that supplementation with magnesium sulfate might be positively associated with the mortality of septic patients. Although there is an ongoing argument that mild hypermagnesemia may be beneficial to patients because of the anti-inflammatory, antioxidant, and anti-apoptotic effects of Mg[32, 33], we still emphasize that clinical physicians should be cautious about Mg oversupplementation in septic patients. Since kidneys are vulnerable during sepsis[30], and patients with kidney function impairment are at risk for severe hypermagnesemia if large doses of Mg are given[20], supplementation could cause poor manifestations. In addition, we could not analyze the bolus speed and doses of $MgSO_4$ supplementation or the timing of subsequent Mg concentration monitoring, and we can only speculate that the speed and doses may affect the relationship between Mg levels and mortality. Of note, serum Mg levels do not correlate well with total body stores, as the majority are intracellular, and serum concentrations may be transiently elevated for a few hours after administration of an IV dose[29]. Therefore, we suggest that Mg levels should be measured daily or more frequently and be controlled more strictly in septic patients receiving magnesium sulfate therapy.

There are some limitations of this study. First, we could only evaluate serum Mg levels during the whole ICU stay due to the lack of total reported Mg and ionized Mg levels. Some studies revealed that ionized Mg might be a more physiologically relevant marker than total Mg levels[10, 34, 35]. Studies on total Mg and ionized Mg in septic patients should be performed to further disclose the relationship between Mg levels and mortality rates. Second, we did not take into consideration the association between Mg abnormalities and acute kidney injury. Third, we did not analyze the degree of hypo- or hypermagnesemia, or the relevant poor outcomes, since patients with different degrees of hypo- or hypermagnesemia may exhibit different symptoms and thus have various prognoses. Fourth, this study was observational and could not demonstrate the causal-relationship between Mg levels and outcome. Fifth, although we adjusted for potential confounding factors, there might also be residual confounding factors. Sixth, as we can see in spline analysis, the confidence intervals were wide at higher magnesium due to its sparse sample size. Thus, the results with extreme levels of potassium should be interpreted with caution.

Conclusion

Hypermagnesemia was significantly associated with higher risk of 28-day and 90-day mortality. After supplementation with magnesium sulfate, the subsequent hypomagnesemia and hypermagnesemia were associated with increased mortality, suggesting that we should be cautious about Mg oversupplementation and be more rigorous to monitor Mg levels.

Declarations

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and consent was obtained for the original data collection. Thus, the ethical approval statement and the need for informed consent were waived.

Consent for publication

Not applicable

Availability of data and materials

Data in the article can be obtained from MIMIC-IV database(0.4version) (<https://mimic.physionet.org/>)

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LL and QH conducted data extraction. SZ, HH and JW conducted statistical analysis. ZZ and SA designed the study and wrote the manuscript. ZC analyzed and interpreted the result. All authors read and approved the final manuscript.

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Tables

Table 1 Baseline Characteristics of patients in the study

var	Total (n=8175)	Survival(n=6790)	Death(n=1385)	P
Age, yr	68.94(57.08-80.41)	68.17(56.30-79.85)	72.47(61.36-82.70)	<0.001
Male, %	5210(63.73)	4331(63.78)	879(63.47)	0.822
Admission type, emergency, %	4122(50.42)	3419(50.35)	703(50.76)	0.784
Non-white, %	2780(34.01)	2265(33.36)	515(37.18)	0.006
Married, %	3283(40.16)	2724(40.12)	559(40.36)	0.866
Medicare, %	4692(57.39)	3856(56.79)	836(60.36)	0.014
Respiratory rate (/min)	19.81(17.27-22.77)	19.45(17.09-22.31)	21.57(18.61-24.84)	<0.001
Heart rate (bpm)	87.54(76.53-100.08)	86.74(75.96-98.88)	92.48(80.15-106.58)	<0.001
Temperature (°C)	36.86(36.59-37.22)	36.88(36.62-37.23)	36.77(36.4-37.18)	<0.001
MAP mmHg	77.36(71.87-84.94)	78.05(72.57-85.64)	73.99(68.33-80.89)	<0.001
Weight kg	77.15(64.4-94)	77.4(64.99-94.64)	75.8(62.6-92)	<0.001
Lactate (mmol/L)	1.9(1.3-2.9)	1.73(1.25-2.5)	2.8(1.75-4.99)	<0.001
SpO2 (%)	96.93(95.54-98.28)	97.00(95.69-98.30)	96.44(94.52-98.19)	<0.001
WBC (×10 ⁹)	11.95(8.33-16.7)	11.7(8.3-16.25)	13.4(8.58-19.49)	<0.001
Platelets (×10 ⁹)	195.75(134-272.5)	200(141-275.19)	170(96.67-258)	<0.001
Creatinine (mg/dL)	1.12(0.8-1.83)	1.05(0.75-1.68)	1.6(1-2.55)	<0.001
Hemoglobin (mg/dL)	10.2(8.93-11.7)	10.3(9-11.75)	9.8(8.5-11.39)	<0.001
Chloride (mmol/L)	103.67(99.67-107.5)	103.75(100-107.5)	103.33(98.6-108)	0.140
Calcium (mg/dl)	8.2(7.7-8.7)	8.2(7.7-8.7)	8.08(7.55-8.6)	<0.001
Potassium (mmol/L),	4.13(3.78-4.55)	4.1(3.77-4.5)	4.28(3.86-4.83)	<0.001
Sodium (mmol/L),	138(135-141)	138(135.33-140.89)	138(134.5-141.67)	0.409
BUN (mg/dl),	24.33(15-40.67)	22.5(14.5-37.25)	34.86(22-54.2)	<0.001
Bicarbonate (mmol/L)	22.33(19.33-25.25)	22.67(20-25.5)	20.25(16.5-24)	<0.001

Daily urine output, (L/d)	1.38(0.81-2.2)	1.5(0.93-2.32)	0.77(0.28-1.43)	<0.001
SAPS-II	33(25-42)	31(24-39)	44(35-54)	<0.001
SOFA	4(3-6)	4(2-6)	6(4-8)	<0.001
CCI	6(4-8)	5(4-8)	7(5-9)	<0.001
GCS	14(10-15)	14(11-15)	10(5-14)	<0.001
Baseline magnesemia				
Magnesemia, mg/dL	1.9(1.7-2.2)	1.9(1.7-2.1)	2.0(1.7-2.3)	<0.001
Hypermagnesemia, %	841(10.29)	641(9.44)	200(14.44)	<0.001
Hypomagnesemia, %	1870(22.87)	1609(23.70)	261(18.84)	
Normomagnesemia, %	5464(66.84)	4540(66.86)	924(66.71)	
VENT, n (%)	3941(48.21)	2924(43.06)	1017(73.43)	<0.001
CRRT, n (%)	384(4.70)	180(2.65)	204(14.73)	<0.001
VASO, n (%)	3575(43.73)	2587(38.10)	988(71.34)	<0.001
AKI, n (%)	5795(70.89)	4537(66.82)	1258(90.83)	<0.001
Magnesium Sulfate, n (%)	5113(62.54)	4248(62.56)	865(62.45)	0.940
Infection site, %				
Blood	2593(31.72)	2070(30.49)	523(37.76)	<0.001
Lung	432(5.28)	312(4.59)	120(8.66)	<0.001
Stool	131(1.60)	96(1.41)	35(2.53)	0.003
Urine	3203(39.18)	2648(39.00)	555(40.07)	0.456
Other	2661(32.55)	2281(33.59)	380(27.44)	<0.001

Continuous variables are reported as median (interquartile range [IQR]).

MAP: mean arterial pressure, WBC: white blood cells, BUN: Urea Nitrogen, CCI: Charlson comorbidity index, VENT: ventilation, CRRT: continuous renal replacement therapy, VASO: vasopressor, AKI: acute kidney injury.

Table 2 Association of mortality and magnesium levels with time-dependent Cox model.

Model	Magnesium status	28-day mortality		90-day mortality	
		HR (95%CI)	P	HR (95%CI)	P
Model 1	Normal	1.00		1.00	
	Hypo-	1.01(0.81-1.25)	0.951	1.01(0.82-1.25)	0.916
	Hyper-	1.68(1.47-1.91)	<0.001	1.64(1.44-1.87)	<0.001
Model 2	Normal	1.00		1.00	
	Hypo-	1.05(0.84-1.31)	0.666	1.05(0.84-1.29)	0.685
	Hyper-	1.67(1.47-1.91)	<0.001	1.63(1.43-1.86)	<0.001
Model 3	Normal	1.00		1.00	
	Hypo-	1.09(0.86-1.37)	0.486	1.06(0.85-1.34)	0.573
	Hyper-	1.42(1.23-1.64)	<0.001	1.42(1.24-1.64)	<0.001

Model 1: unadjusted

Model 2: adjusted age, gender, admission type, ethnicity, marital status, insurance

Model 3: further adjusted for MAP, weight, MgSO₄ supplement, VENT, CRRT, VASO, AKI, daily urine output, hemoglobin, potassium, platelets, WBC, chloride, lactate, sodium, creatinine, bicarbonate, heartrate, resp rate, temperature, SpO₂, BUN, infection site.

Table 3 The association of magnesium and 28-day mortality pre- and post- magnesium sulfate supplement.

		Pre-MgSO ₄ supplement		Post-MgSO ₄ supplement	
Correction	Status	HR (95%CI)	P	HR (95%CI)	P
28-day mortality					
Model 1	Normal	1.00		1.00	
	Hypo-	1.08(0.93-1.26)	0.325	1.22(0.94-1.59)	0.128
	Hyper-	1.28(1.02-1.60)	0.036	1.69(1.40-2.03)	<0.001
Model 2	Normal	1.00		1.00	
	Hypo-	1.07(0.92-1.25)	0.362	1.34(1.03-1.73)	0.028
	Hyper-	1.27(1.01-1.60)	0.045	1.68(1.39-2.02)	<0.001
Model 3	Normal	1.00		1.00	
	Hypo-	0.98(0.83-1.15)	0.795	1.51(1.15-1.99)	0.003
	Hyper-	1.00(0.76-1.31)	0.984	1.44(1.17-1.78)	0.001
90-day mortality					
Model 1	Normal	1.00		1.00	
	Hypo-	1.09(0.93-1.26)	0.287	1.23(0.96-1.58)	0.108
	Hyper-	1.22(0.97-1.55)	0.093	1.66(1.37-2.00)	<0.001
Model 2	Normal	1.00		1.00	
	Hypo-	1.08(0.93-1.26)	0.312	1.34(1.05-1.72)	0.021
	Hyper-	1.21(0.96-1.54)	0.109	1.64(1.36-1.98)	<0.001
Model 3	Normal	1.00		1.00	
	Hypo-	0.98(0.82-1.17)	0.792	1.53(1.18-1.99)	0.001
	Hyper-	0.98(0.75-1.28)	0.881	1.43(1.16-1.77)	0.001

Model 1: unadjusted

Model 2: adjusted age, gender, admission type, ethnicity, marital status, insurance

Model 3: further adjusted for MAP, weight, MgSO₄ supplement, VENT, CRRT, VASO, AKI, daily urine output, hemoglobin, potassium, platelets, WBC, chloride, lactate, sodium, creatinine, bicarbonate, heartrate, resp rate, temperature, SpO₂, BUN, infection site.

Figures

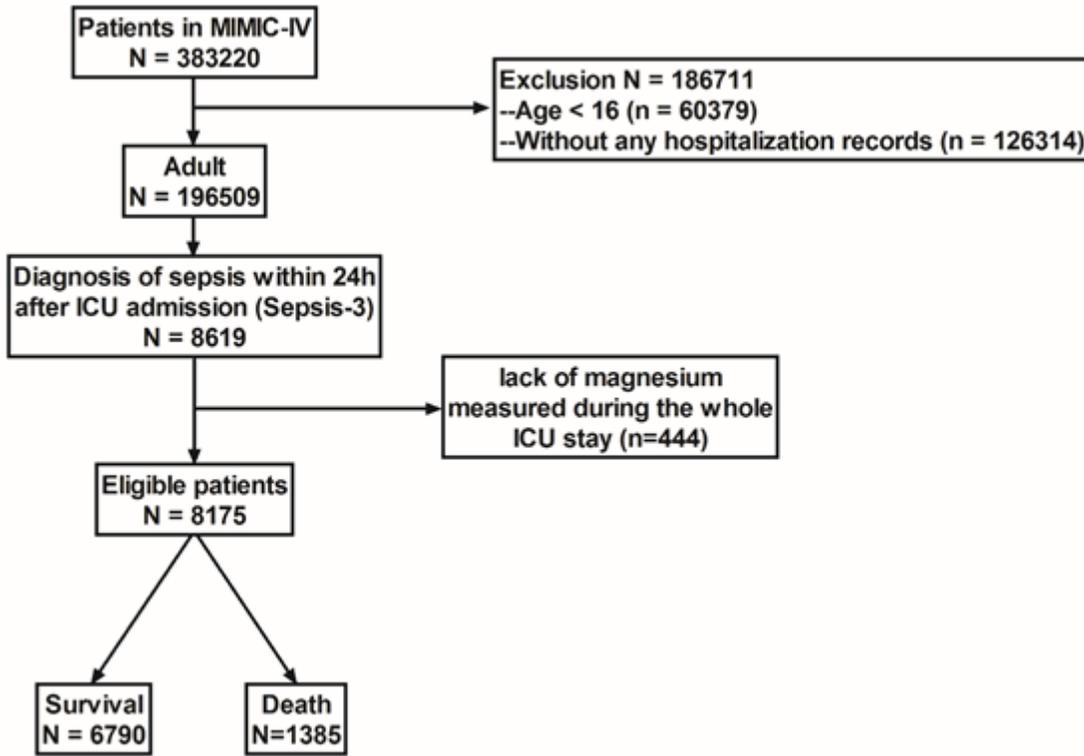


Figure 1

Flowchart of patients in the study.

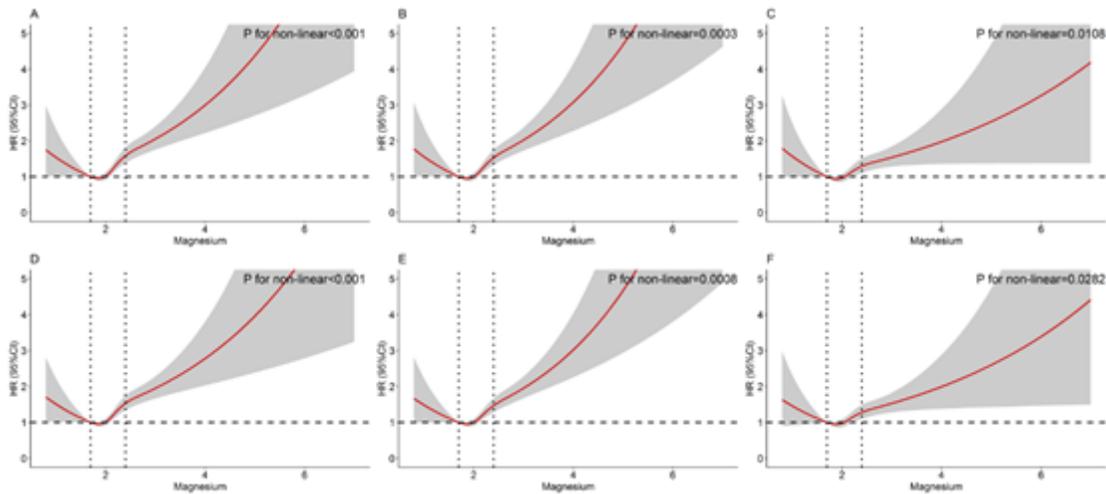


Figure 2

Association of mortality and continuous magnesium levels with restricted cubic splines in time-dependent Cox model. Model 1: unadjusted Model 2: adjusted age, gender, admission type, ethnicity, marital status, insurance Model 3: further adjusted for MAP, weight, MgSO₄ supplement, VENT, CRRT, VASO, AKI, daily urine output, hemoglobin, potassium, platelets, WBC, chloride, lactate, sodium, creatinine, bicarbonate, heartrate, resp rate, temperature, SpO₂, BUN, infection site. Dotted line denoted the normal range of magnesium in populations (1.7-2.4 mg/dl).

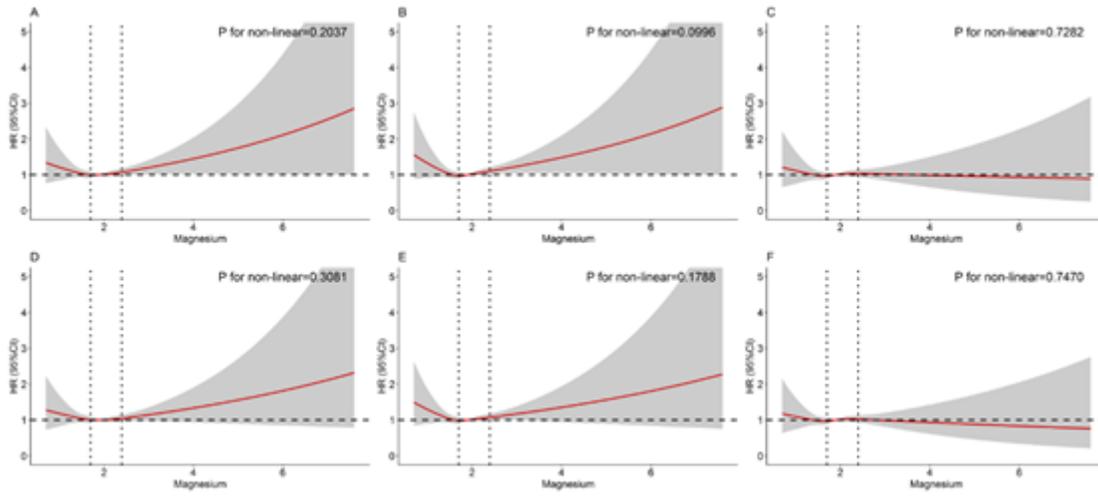


Figure 3

the association between mortality and magnesium levels pre-MgSO₄ supplement. Model 1: unadjusted Model 2: further adjusted age, gender, admission type, ethnicity, marital status, insurance Model 3: further adjusted for MAP, weight, MgSO₄ supplement, VENT, CRRT, VASO, AKI, daily urine output, hemoglobin, potassium, platelets, WBC, chloride, lactate, sodium, creatinine, bicarbonate, heartrate, resp rate, temperature, SpO₂, BUN, infection site. Dotted line denoted the normal range of magnesium in populations (1.7-2.4 mg/dl).

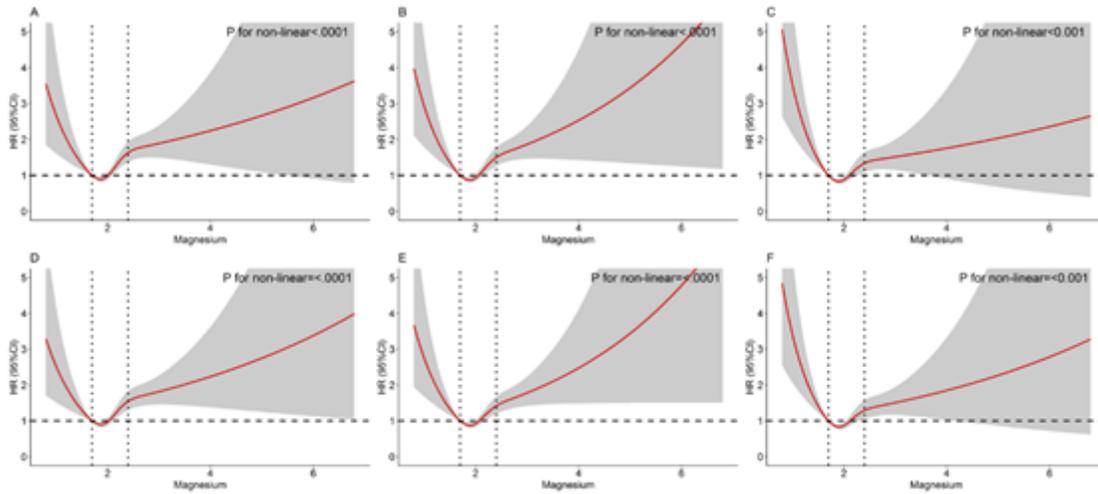


Figure 4

the association between mortality and magnesium post-MgSO₄ supplement. Model 1: unadjusted Model 2: adjusted age, gender, admission type, ethnicity, marital status, insurance Model 3: further adjusted for MAP, weight, MgSO₄ supplement, VENT, CRRT, VASO, AKI, daily urine output, hemoglobin, potassium, platelets, WBC, chloride, lactate, sodium, creatinine, bicarbonate, heartrate, resp rate, temperature, SpO₂, BUN, infection site. Dotted line denoted the normal range of magnesium in populations (1.7-2.4 mg/dl).