Effect of Hypomagnesemia On The Prognosis of Patients With Sepsis in ICU: A Retrospective Cohort Study

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Abstract

Objective

Existing studies have shown that the incidence of hypomagnesemia may be as high as 60%. However, the correlation between hypomagnesia and sepsis mortality remains elusive. The current study evaluated the effect of hypomagnesemia on the prognosis of patients with sepsis in ICU.

Methods

It was a retrospective cohort study based on an online database named MIMIC III. A total of 1448 sepsis patients with serum magnesium were admitted to the database, among which 645 patients were screened out.

Results

At 28 days, 99 patients (30.84%) in the hypomagnesemia group and 123 patients (38.0%) (P = 0.06) in the non-hypomagnesemia group died. There was no correlation between hypomagnesemia and 28-day mortality in patients with sepsis (HR = 1.07; P = 0.87, 95% CI). However, the duration of mechanical ventilation (P < 0.01), the duration of vasoactive drug use (P < 0.01), the length of ICU stay (P < 0.01), and the length of hospital stay (P < 0.01) of patients in the hypomagnesemia group were higher than those in the non-hypomagnesemia group. In the subgroup analysis, the time of no vasopressor (P < 0.01) and the time of no mechanical ventilation (P < 0.01) in the magnesium supplementation group were significantly longer than those in the non-magnesium supplementation group. More importantly, the 14-day mortality (30.8% vs 48.9%, P < 0.01) and 28-day mortality (33.8% vs 48.9%, P = 0.03) in patients with magnesium supplementation were lower than patients without magnesium supplementation.

Conclusions

For sepsis patients in ICU, although hypomagnesemia had no significant correlation with 28-day mortality, it still prolonged the duration of mechanical ventilation and vasoactive drug use, and increased the length of ICU stay and hospital stay. Even for patients with normal serum magnesium levels, optimizing serum magnesium levels may improve the prognosis of patients with sepsis.

Introduction

Electrolyte disturbance is common in critically ill patients. The deterioration of clinical prognosis caused by plasma disturbance of potassium, sodium, chlorine, and calcium has been widely considered by clinicians. However, magnesium abnormality has not received enough concerns, which is known as “forgotten ions”. The current knowledge has indicated that the incidence of hypomagnesemia may be as

high as 60% or above in severe patients due to intestinal dysfunction, renal insufficiency, fluid resuscitation, nutritional disorder, drugs, and other reasons[1–2]. Magnesium ions play an important role in the human body. In addition to the regulation of electrolyte stability, magnesium ions are also widely involved in muscle activity, lactic acid metabolism, immune response, and even blood pressure regulation[3]. The previous study has identified hypomagnesemia as a risk factor for increased mortality in sepsis patients[4]. However, some controlled studies or systematic retrospective studies have not reached similar conclusions [5]. Based on Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC III) database, this study analyzed 645 sepsis patients in the intensive care unit (ICU) to evaluate the effect of hypomagnesemia on the prognosis of sepsis patients.

Materials And Methods

Database introduction

MIMIC III, a multi-parameter intelligent monitoring database maintained by the Massachusetts Institute of Technology (Cambridge, Massachusetts, USA) and Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA), enrolls 61,532 ICU inpatients including 53,432 adult patients and 8,100 neonatal patients. The data in this study were extracted using Postgre SQL 9.5 software. One of the researchers, Chengwei Lv, has completed the online training course at the National Institutes of Health (certification number: 39524425). The original data were collected with the consent of the patients or guardians and were not intended specifically for this study.

Patient and Public Involvement

No patient involved.

Inclusion and exclusion criteria

Inclusion criteria were as follows: sepsis patients admitted to the Beth Israel Deaconess Medical Center from June 2001 to October 2012, hospitalization time ≥ 48 hours, and the presence of serum magnesium concentration data during ICU stay.

Exclusion criteria were as follows: patients with chronic kidney disease, cerebrovascular accident, malignant tumor, or diabetic ketoacidosis (DKA), puerperal women, under the age of 18, use of magnesium supplements prior to admission. (Fig. 1)

Methods

Patients with serum magnesium concentration ≤ 1.7 mg/dL during ICU stay were included in the hypomagnesemia group, and patients with the minimum serum magnesium concentration > 1.7 mg/dL during ICU stay were included in the non-hypomagnesemia group. The following information was extracted: gender, age, BMI, serum levels of Na^+, K^+, and Ca^{2+}, blood glucose, creatinine, lactic acid, whether mechanical ventilation and duration of mechanical ventilation, Sequential Organ Failure

Assessment (SOFA) score, Glasgow Coma Scale (GCS) score, SAPSII score at the time of admission to ICU, and complications during ICU such as chronic obstructive pulmonary disease, coronary heart disease, hypertension, diabetes, heart failure, and acute kidney injury (AKI).

Outcomes

The primary endpoint was 28-day mortality. The secondary endpoints included ICU mortality, hospital mortality, the proportion of mechanical ventilation, and the duration of no mechanical ventilation.

Statistical analysis

Univariate analysis was performed on the patients in the hypomagnesemia group and non-hypomagnesemia group. Continuous variables were analyzed using the Student's *t* test and expressed in the tables as mean ± standard deviation (SD). Continuous variables of non-normal distribution were analyzed using the chi-square test and expressed as median ± quartile. All tests were two-sided and a value of $P < 0.05$ was considered significant.

To better demonstrate the effect of hypomagnesemia on the outcomes of sepsis patients, we performed multivariate logistic regression analysis, ordinary least squares (OLS) regression analysis, and proportional risk regression model (Cox model) analysis. All the variables with $P < 0.2$ from the univariate analysis were input into the stepwise multiple regression model. Results are presented as odds ratios (OR) and 95% confidence intervals (CI). All statistical analyses were performed using the software Stata 16.0.

Results

Baseline characteristics

The MIMIC III database contains the admission records of 4085 sepsis patients, of which 2637 were excluded due to the absence of serum magnesium data during hospitalization. Of the remaining 1448 inpatients, 803 patients were excluded because of puerperium (1), chronic kidney disease (311), cerebrovascular accident (5), malignant tumor (8), DKA (270), use of magnesium before hospitalization (140), hospital stay ≤ 48 h (5), and survival time in ICU ≤ 48 h (63). After excluding outliers, 645 hospitalized patients were recruited in this study, including 321 patients with hypomagnesemia and 324 patients with non-hypomagnesemia. The median age was 65.8 [52.8, 79.9] years, and 341 cases (52.87%) were male. The most common baseline diseases were AKI (419; 64.96%), hypertension (308; 47.75%), and heart failure (150; 23.26%). There was a statistically significant difference in age between the two groups ($P < 0.01$). In addition, the number of septic shock patients between the two groups was also statistically different. The number of patients with hypomagnesemia [229 (71.34%)] was significantly higher than that without hypomagnesemia [205 (63.27%), $P = 0.03$]. The concentration of serum magnesium, potassium, and calcium and the level of creatinine of patients with hypomagnesemia at admission were significantly lower than those of patients without hypomagnesemia. Other baseline

characteristics were similar between the two groups. The demographic characteristics of the hypomagnesemia group and the non-hypomagnesemia group are shown in Table 1.

Table 1
Base line

Variable	Total(n = 645)	Hypomagnesemia group(n = 321)	Non-hypomagnese-mia group(n = 324)	P;95%CI
Age(IQR)	65.8[52.8,79.9]	63.2[51.8,76.6]	68.7[53.9,82.0]	< 0.01
Male,n(%)	341(52.87)	160(49.84)	181(55.86)	= 0.13
BMI(IQR)	27.1[23.1,31.6]	27.1[22.7,31.2]	27.0[23.6,32.0]	= 0.37
SOFA(IQR)	7[4, 10]	7[4, 10]	7[4, 9]	= 0.86
Day 1 GCS score(IQR)	15[13,15]	15[14,15]	15[13,15]	= 0.06
SAPS II(IQR)	44[34,55]	44[34,54]	44[34,55]	= 0.87
Complication,n(%)				
COPD	11(1.71)	4(1.25)	7(2.16)	= 0.37
Coronary heart disease	99(15.35)	44(13.71)	55(16.98)	= 0.25
Hypertension	308(47.75)	146(45.48)	162(50)	= 0.25
AKI	419(64.96)	202(62.93)	217(66.98)	= 0.28
Diabetes	51(7.91)	24(7.48)	27(8.33)	= 0.69
Congestive heart failure	150(23.26)	70(21.81)	80(24.69)	= 0.39
Severe sepsis	643(99.69)	321(100)	322(99.38)	= 0.16
Septic shock	434(67.29)	229(71.34)	205(63.27)	= 0.03
Laboratory tests on admission				
Serum magnesium (mg/dL)(IQR)	1.9[1.6,2.2]	1.6[1.4,1.8]	2.1[1.9,2.3]	< 0.01
Scr (mg/dL)(IQR)	1.1[0.8,1.8]	1[0.7,1.6]	1.3[0.9,2.0]	< 0.01
Blood glucose (mg/dL)(IQR)	121[100,155]	119[97,155]	122[103,155]	= 0.61
Platelet (K/uL)(IQR)	194[120,283]	188[121,272]	204[119,293]	= 0.36

Note: BMI: Body Mass Index; SOFA: Sequential Organ Failure Assessment; GCS; Glasgow Coma Scale;SAPSII: Simplified Acute Physiology Score; COPD□Chronic Obstructive Pulmonary Disease; AKI: Acute Kidney Injury.

Variable	Total(n = 645)	Hypomagnesemia group(n = 321)	Non-hypomagnese-mia group(n = 324)	P;95%CI
Serum potassium (mEq/L)(IQR)	3.9[3.5,4.4]	3.8[3.5,4.4]	4[3.6,4.4]	< 0.01
Serum sodium (mEq/L)(IQR)	138[134,142]	138[135,141]	139[134,142]	= 0.58
Lactate level (mmol/L)(IQR)	1.9[1.3,3]	2[1.3,3.1]	1.8[1.2,2.8]	= 0.08
Blood calcium (mmol/L)(IQR)	1.9[1.7,2.0]	1.8[1.6,1.9]	1.9[1.8,2.1]	< 0.01
Hypokalemia,n(%)	474(73.49)	255(79.44)	219(67.59)	< 0.01
Hyponatremia,n(%)	384(59.53)	200(62.31)	184(56.79)	= 0.15
Hypocalcemia,n(%)	641(99.38)	320(99.69)	321(99.07)	= 0.32
Outcome index				
Vasopressor use ,n(%)	457(70.85)	235(73.21)	222(68.52)	= 0.19
MV use,n(%)	420(65.12)	228(68.54)	192(59.26)	= 0.01
Vasopressor time (h)(IQR)	26.8[0,83.4]	34.4[0,86.7]	20.2[0,76.6]	= 0.02
MV time(h)(IQR)	45.7[0,185]	70.1[0,219]	26.3[0,156.9]	< 0.01
ICU stays (h)(IQR)	120[63,266]	145[71,296]	106[57.5,228]	< 0.01
hospital stays (h) (IQR)	311[167,533]	341[188,628]	280[146.5,468]	< 0.01
In-ICU mortality ,n(%)	125(19.4)	52(16.2)	73(22.53)	= 0.04
In-hospital mortality,n(%)	177(27.44)	79(24.61)	98(30.25)	= 0.11

Note: BMI: Body Mass Index; SOFA: Sequential Organ Failure Assessment; GCS; Glasgow Coma Scale;SAPSII: Simplified Acute Physiology Score; COPD□Chronic Obstructive Pulmonary Disease; AKI: Acute Kidney Injury.

Variable	Total(n = 645)	Hypomagnesemia group(n = 321)	Non-hypomagnese-mia group(n = 324)	P;95%CI
14-day mortality ,n(%)	211(32.7)	95(29.6)	116(35.8)	= 0.09
28-day mortality ,n(%)	222(34.4)	99(30.84)	123(38.0)	= 0.06
60-day mortality ,n(%)	240(37.21)	113(35.2)	127(39.2)	= 0.29

Note: BMI: Body Mass Index; SOFA: Sequential Organ Failure Assessment; GCS; Glasgow Coma Scale;SAPSII: Simplified Acute Physiology Score; COPD□Chronic Obstructive Pulmonary Disease; AKI: Acute Kidney Injury.

Primary and secondary study endpoints

For the primary study endpoint, a total of 222 patients in the two groups died at 28 days, including 99 (30.84%) patients in the hypomagnesemia group and 123 (38.0%) patients in the non-hypomagnesemia group. There was no statistical difference in 28-day mortality between the two groups (P = 0.06). To further investigate the correlation between hypomagnesemia during hospitalization and 28-day mortality, we conducted the multivariate analysis with the Cox proportional-hazards model to estimate the simultaneous effects of prognostic factors on 28-day mortality (Table 2) and plotted the Kaplan-Meier (K-M) curve. After survival analysis, we found that hypomagnesemia during hospitalization had no significant effect on 28-day mortality (P = 0.87, 95% CI). K-M curve shows the number of patients who survived at 7/14/21/28 days after discharge from the hospital in the two groups (Fig. 2).

Table 2
Cox proportional hazards regression model

	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]
Hypomagnesemia	1.07	0.41	0.16	0.87	0.50–2.28

Note: Cox regression analysis excluded age, gender, body weight, complications (severe sepsis, septic shock), admission GCS score, creatinine level at admission, lactic acid level at admission, serum magnesium concentration at admission, serum potassium concentration at admission, serum calcium concentration at admission and other influential factors.

Among the secondary study endpoints, hypomagnesemia significantly affected the use of mechanical ventilation (P = 0.01), duration of mechanical ventilation (P < 0.01) and vasoactive drug use (P < 0.01), ICU time (P < 0.01), length of hospital stay (P < 0.01), ICU mortality (P = 0.04), and hypokalemia during

hospitalization (P < 0.01). Multivariate regression analysis was performed on these indicators, and logistic regression analysis was conducted to investigate whether there were significant differences in hypokalemia and ICU mortality between the two groups. The results were expressed in OR and 95% CI. OLS multiple linear regression was performed on the duration of vasoactive drug use and mechanical ventilation, ICU time, and the length of hospital stay (Table 3). After controlling the related factors, the effect of hypomagnesemia on ICU mortality was no longer significant (P = 0.71), but its effect on other prognostic indicators remained statistically significant. The hypomagnesemia group had a higher proportion of hypokalemia compared with the non-hypomagnesemia group; the length of ICU and hospital stay, and the duration of vasoactive drug use and mechanical ventilation in the hypomagnesemia group were longer than those in the non-hypomagnesemia group (all P < 0.01). We made histograms of the average ICU time (Figure A) and average hospital stay (Figure B) for different magnesium levels (Fig. 3). It could be seen that with the gradual increase of the minimum serum magnesium concentration during hospitalization, the length of ICU and hospital stay generally showed a downward trend.

Table 3
Multivariate regression analysis of the effect of hypomagnesemia on related outcomes of patients with sepsis

Variable	Hypomagnesemia group	Non-hypomagnesemia group	Univariate P-value;95%CI	Multivariate P-value;95%CI
Hypokalemia,n(%)	255(79.44)	219(67.59)	< 0.01	< 0.01 OR:0.43;[0.25–0.72]
Vasopressor time (h)（IQR）	34.4[0,86.7]	20.2[0,76.6]	= 0.02	< 0.01 coef: -27.59[-46.35 - -8.84]
MV time(h)（IQR）	70.1[0,219]	26.3[0,156.9]	< 0.01	< 0.01 coef: -72.48[-110.41 - -34.54]
ICU stays (h)（IQR）	145[71,296]	106[57.5,228]	< 0.01	< 0.01 coef: -66.24; [-107.80 - -24.67]
hospital stays (h)（IQR）	341[188,628]	280[146.5,468]	< 0.01	< 0.01 coef: -140.55; [-213.45–67.65]
In-ICU mortality (n（%）)	52(16.2)	73(22.53)	= 0.04	= 0.71 OR: 1.11;[0.64–1.91]

Note: Age, gender, complications (severe sepsis, septic shock), admission GCS score, creatinine level at admission, lactic acid level at admission, serum magnesium concentration at admission, serum potassium concentration at admission, serum calcium concentration at admission were excluded in multivariate regression analysis.

Subgroup analyses

To observe the effect of magnesium supplementation on the prognosis of patients with non-hypomagnesemia sepsis, we further analyzed 324 patients with non-hypomagnesemia. These patients were assigned to two groups according to whether they were supplemented with magnesium during hospitalization. The patients without magnesium supplementation (no magnesium supplement was prescribed by doctors during hospitalization) were included in group A, and the patients with magnesium supplementation (magnesium supplement was prescribed by doctors during hospitalization, regardless

of frequency and dosage) were included in tgroup B. The baseline information of the two groups of patients is shown in Table 4.

Table 4
Subgroup Base line

Variable	A group(n = 90)	B group(n = 234)	P-value;95%CI
Age(IQR)	68.9[54.2,82.5]	68.5[53.7,81.9]	= 0.64
Male,n(%)	47(52.2)	134(57.3)	= 0.41
BMI(IQR)	24.7[22.0,30.8]	28.0[24.4,32.3]	= 0.01
SOFA(IQR)	6[4, 10]	7[4, 9]	= 0.62
Day 1 GCS score(IQR)	15[13,15]	15[13,15]	= 0.56
SAPS II(IQR)	44[35,58]	44[34,54]	= 0.43
Complication,n(%)			
COPD	1(1.1)	6(2.6)	= 0.42
Coronary heart disease	11(12.2)	44(18.8)	= 0.16
Hypertension	39(43.3)	123(52.6)	= 0.14
AKI	65(72.2)	152(65.0)	= 0.21
Diabetes	3(3.3)	24(10.3)	= 0.04
Congestive heart failure	22(24.4)	58(24.8)	= 0.95
Severe sepsis	90(100)	232(99.1)	= 0.38
Septic shock	57(63.3)	148(63.2)	= 0.99
Laboratory tests on admission(IQR)			
Serum magnesium(mg/dL)	2.2[2.1,2.4]	2.1[1.9,2.3]	< 0.01
Scr (mg/dL)	1.4[1,2.5]	1.2[0.8,1.7]	= 0.01
Blood glucose(mg/dL)	118.5[103,162]	122.5[102,152]	= 0.82
Platelet(K/uL)	183[102,264]	210[130,294]	= 0.15
Serum potassium(mEq/L)	4.2[3.8,4.6]	3.9[3.6,4.3]	< 0.01
Serum sodium(mEq/L)	139[134,143]	138[134,142]	= 0.41
Lactate level(mmol/L)	2.1[1.6,3.0]	1.7[1.2,2.8]	= 0.03
Blood calcium(mmol/L)	1.98[1.85,2.12]	1.92[1.77,2.07]	= 0.05
Others			
Vasopressor use ,n(%)	52(57.8)	170(72.6)	= 0.01
MV use,n(%)	45(50)	147(62.8)	= 0.04

Univariate analysis and multivariate regression analysis of patients in the two groups showed that the proportion of patients using vasoactive drugs and requiring mechanical ventilation in group B was higher than that in group A; moreover, the duration of free vasoactive drug use (P < 0.01) and free mechanical ventilation (P < 0.01) in group B was significantly longer than that in group A. In addition, the 14-day mortality (P < 0.01) and 28-day mortality (P = 0.03) of patients in group B were significantly lower than those in group A (Fig. 4**).** Although there was no statistical significance in 60-day mortality between the two groups, the 60-day mortality of patients in group B during hospitalization was lower than that of patients in group A (Table 5**)**.

Table 5
Multiple regression analysis of the effect of magnesium supplementation on prognosis in patients with non-hypomagnesemia sepsis

Variable	**A group (n = 90)**	**B group (n = 234)**	**Univariate P-value;95%CI**	**Multivariate P-value;95%CI**
Vasopressor free time(IQR)(h)	51.6[30.8,94]	72.4[40.8,171.6]	< 0.01	< 0.01 Coef:49.34;[13.68–84.99]
MV free time(IQR)(h)	46.5[28,68]	59.7[34.1,97.8]	< 0.01	< 0.01 Coef:24.35;[8.48–40.23]
14-day mortality ,n(%)	44(48.9)	72(30.8)	< 0.01	< 0.01 OR:0.47;[0.27–0.82]
28-day mortality ,n(%)	44(48.9)	79(33.8)	= 0.01	= 0.03 OR:0.55;[0.32–0.95]
60-day mortality ,n(%)	44(48.9)	83(35.5)	= 0.03	= 0.08 OR:0.61;[0.35–1.05]

Note: Multivariate regression analysis excluded possible influencing factors, including BMI, coronary heart disease, hypertension, diabetes mellitus, platelet level at admission, creatinine level at admission, lactate level at admission, serum magnesium concentration at admission, serum potassium concentration at admission, serum calcium concentration at admission and other influencing factors.

Discussion

Retrospective analysis of previous studies has shown that hypomagnesemia can prolong ventilator support and hospital stay and increased mortality in critically ill patients [5]. Animal studies have demonstrated the involvement of magnesium ions in the immunomodulatory response of sepsis patients, and intriguingly, magnesium ion supplementation may contribute to the prognosis of sepsis patients [6]. Nevertheless, relatively little is known about the exact effects of hypomagnesemia and magnesium supplementation on the outcomes of sepsis patients. Therefore, we used the MIMIC database to retrospectively analyze the effect of hypomagnesemia on sepsis patients.

This study found that the patients with hypomagnesemia were younger (63.2 vs 68.7), had a higher proportion of septic shock (71.34% vs 73.27%, P = 0.03), and also had lower levels of serum potassium, serum calcium, and creatinine at admission (all P < 0.01). Preliminary analysis revealed that the duration of vasoactive drug use and mechanical ventilation and the length of ICU stay and the total hospital stay of patients with hypomagnesemia were longer. The ICU mortality of patients with hypomagnesemia was higher (P = 0.04), but no statistical difference was observed between the two groups after multivariate regression analysis. Similarly, there were no significant differences in 28-day mortality, hospital mortality, 14-day mortality, or 60-day mortality between the two groups, even after multivariate regression analysis. According to K-M survival curve analysis, there was no statistical difference in 28-day mortality, the main endpoint of the study, between the two groups (Fig. 2), which is inconsistent with the previous study on critically ill patients [7]. A retrospective study involving 10 clinical studies has indicated that hypomagnesemia serves as a risk factor for increased mortality in critically ill patients, but it does not exert any effect on the risk of sepsis [8], which may reflect the particularity and complexity of sepsis patients compared with critically ill patients. Multivariate regression analysis demonstrated that the patients with hypomagnesemia had a higher incidence of hypokalemia (P < 0.01). The decrease of serum potassium level caused by low magnesium is attributed to a combination of multiple mechanisms, one of which is that magnesium modulates the activity of the ROMK channel (potassium channel in the outer renal medulla), leading to increased potassium excretion from the kidney [9]. C. Thongprayoon has found that hypomagnesemia on admission increases the incidence of acute respiratory failure during hospitalization [10]. Consistently, we found that the duration of mechanical ventilation in patients with hypomagnesemia was significantly longer than that in patients without hypomagnesemia (70.1 vs 26.3, P < 0.01). This may be related to respiratory muscle weakness caused by hypomagnesemia [10]. In addition, magnesium regulates the contractibility of smooth muscle cells, and hypomagnesemia leads to bronchospasm, which in turn prolongs mechanical ventilation [11]. Our study found that the duration of vasoactive drug use in patients with hypomagnesemia was longer than that in patients without hypomagnesemia, however, the pathological mechanism remained unclear. Intriguingly, magnesium ions are also involved in endothelium-dependent and non-endothelium-dependent vascular tone regulation mechanisms in the microcirculation, and hypomagnesemia can lead to heart failure and severe arrhythmia [12], which may be one of the possible reasons. Patients with hypomagnesemia had a longer duration of mechanical ventilation and vasoactive drug use, which seemed to explain the longer ICU stay and hospital stay of patients with hypomagnesemia (P < 0.01). Also, the length of ICU stay and hospital

stay was decreased with the increase of serum magnesium level **(Fig. 3)**, indicating that the serum magnesium level had an impact on some prognostic indicators of patients with sepsis. Magnesium supplementation in patients with hypomagnesemia is no longer controversial. However, it is not clear whether magnesium supplementation in patients with normal serum magnesium levels can affect the prognosis of sepsis patients. In view of this, we assigned these patients with normal serum magnesium levels to the non-magnesium supplementation group (group A) and magnesium supplementation group (group B) according to whether they were supplemented with magnesium during hospitalization. Despite the differences in basic conditions between the two groups, multivariate regression analysis showed that the 28-day mortality and 14-day mortality of group B were significantly lower than those of group A, but there was no statistically significant difference in 60-day mortality between the two groups. The duration of mechanical ventilation and vasoactive drug use of group B was shorter than that of group A. Similarly, Afsaneh Noormandi performed magnesium supplementation in sepsis patients with normal serum magnesium levels and elucidated that patients with magnesium supplementation had a faster lactic acid clearance and a shorter hospital stay. Although there was no significant difference in 28-day mortality between the two groups of patients, the 28-day mortality of the two groups was significantly lower than that of the placebo group. The average survival time of patients with magnesium supplementation was significantly longer than that of patients treated with placebo [25.85 vs 22.19 days (P = 0.001)] [(4)]. Magnesium ions act as a cofactor of thiamine triphosphatase and participate in lactic acid metabolism. Magnesium iron deficiency may result in the accumulation of lactic acid, which may be the reason why magnesium supplementation improves the prognosis of sepsis patients. These findings suggested that magnesium supplementation for sepsis patients with normal serum magnesium may improve the prognosis.

This study still has some shortcomings. Firstly, the serum magnesium data of all patients were obtained after hospitalization, and there was no fixed specimen collection time. Hence, it failed to analyze the serum magnesium level and the duration of low magnesium before admission, which may affect the results to some extent. Secondly, the reasons, timing, methods, dose, and target magnesium value of magnesium supplementation in patients with normal serum magnesium were not counted. The causal relationship between magnesium supplementation as an intervention and prognosis is not clear, which needs to be further confirmed by high-quality randomized controlled studies.

Conclusion

For sepsis patients admitted to the ICU, although hypomagnesemia has no significant correlation with 28-day mortality, hypomagnesemia can significantly prolong the duration of mechanical ventilation and vasoactive drug use, and increase the length of hospital stay. Even for patients with normal serum magnesium levels, optimizing serum magnesium levels can improve the prognosis of sepsis patients.

Strengths And Limitations Of This Study

►Using an online database named MIMIC III, we conducted a retrospective cohort study of 645 sepsis patients in the intensive care unit (ICU). The large sample size facilitated a robust modelling approach.

►This study did not conduct a statistical analysis of the reasons, timing, methods, doses and target magnesium value of magnesium supplementation, which may have a certain impact on the results.

Abbreviations

MIMIC III
Monitoring in Intensive Care III; ICU:intensive care unit; DKA:diabetic ketoacidosis; BMI:Body Mass Index; SOFA:Sequential Organ Failure Assessment; GCS:Glasgow Coma Scale; SAPSII:Simplified Acute Physiology Score; AKI:acute kidney injury; SD:standard deviation; OLS:ordinary least squares; OR:odds ratios; CI:confidence intervals; COPD:Chronic Obstructive Pulmonary Disease

Declarations

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Not applicable.

Authors' contributions

CL: Responsible for data extraction, analysis and writing of the manuscript. JH: Responsible for data validation. XH: Responsible for study data extraction, validation and analysis. JL: Responsible for study data analysis and manuscript translation.

Ethics approval and consent to participate

Laboratory for Computational Physiology at the Massachusetts Institute of Technology.

Consent for publication

Written informed consent for publication of the case report was obtained from all four patients. A copy of the consents is available for review by the Editor of this journal.

Provenance and peer review

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Availability of data and materials Full data set and materials available from the corresponding author at huxingxing82@163.com. However, reanalysis of the full data need to be approved by MIMIC Institute.

Competing interests

The authors declare that they have no competing interests.

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References

1. Hansen B, Bruserud Ø. Hypomagnesemia in critically ill patients. Journal of Intensive Care 6(1), 2018.
2. Velissaris D, Karamouzos V, Pierrakos C, Aretha D, Karanikolas M. Hypomagnesemia in Critically Ill Sepsis Patients. Journal of Clinical Medicine Research 7(12):911–918, 2015.
3. Thongprayoon C, Cheungpasitporn W, Erickson SB. Admission hypomagnesemia linked to septic shock in patients with systemic inflammatory response syndrome. RENAL FAILURE 37(9):1518–1521, 2015.
4. Noormandi A, Khalili H, Mohammadi M, Abdollahi A. Effect of magnesium supplementation on lactate clearance in critically ill patients with severe sepsis: a randomized clinical trial. EUR J CLIN PHARMACOL 76(2):175–184, 2020.
5. Upala S, Jaruvongvanich V, Wijarnpreecha K, Sanguankeo A. Hypomagnesemia and Mortality in Patients Admitted to Intensive Care Unit: a Systematic Review and Meta analysis. QJM 109(7):453–459, 2016.
6. Wang D, Zheng J, Hu Q, Zhao C, Chen Q, Shi P, Chen Q, Zou Y, Zou D, Liu Q, et al. Magnesium protects against sepsis by blocking gasdermin D N-terminal-induced pyroptosis. Cell Death & Differentiation 27(2):466–481, 2020.
7. Laupland KB, Tabah A, Jacobs N, Ramanan M. Determinants of serum magnesium abnormalities and outcome among admissions to the intensive care unit. ANAESTH CRIT CARE PA 39(6):793–797, 2020.
8. Jiang P, Lv Q, Lai T, Xu F. Does Hypomagnesemia Impact on the Outcome of Patients Admitted to the Intensive Care Unit? A Systematic Review and Meta-Analysis. SHOCK 47(3):288–295, 2017.
9. Ahmed F, Mohammed A. Magnesium: The Forgotten Electrolyte—A Review on Hypomagnesemia. Medical Sciences 7(4):56, 2019.
10. Thongprayoon C, Cheungpasitporn W, Srivali N, Erickson SB. Admission serum magnesium levels and the risk of acute respiratory failure. International journal of clinical practice (Esher) 69(11):1303–1308, 2015.
11. Kılıc H, Kanbay A, Karalezlı A, Babaoglu E, Canan Hasanoglu HC, Erel O, Ates C. The Relationship between Hypomagnesemia and Pulmonary Function Tests in Patients with Chronic Asthma. MED PRIN PRACT 27(2):139–144, 2015.
12. Toprak O, Kurt H, Sari Y, et al. Magnesium Replacement Improves the Metabolic Profile in Obese and Pre-Diabetic Patients with Mild-to-Moderate Chronic Kidney Disease: A 3-Month, Randomised, Double-Blind, Placebo-Controlled Study. Kidney Blood Press Res 42(1):33–42, 2017.

Figures

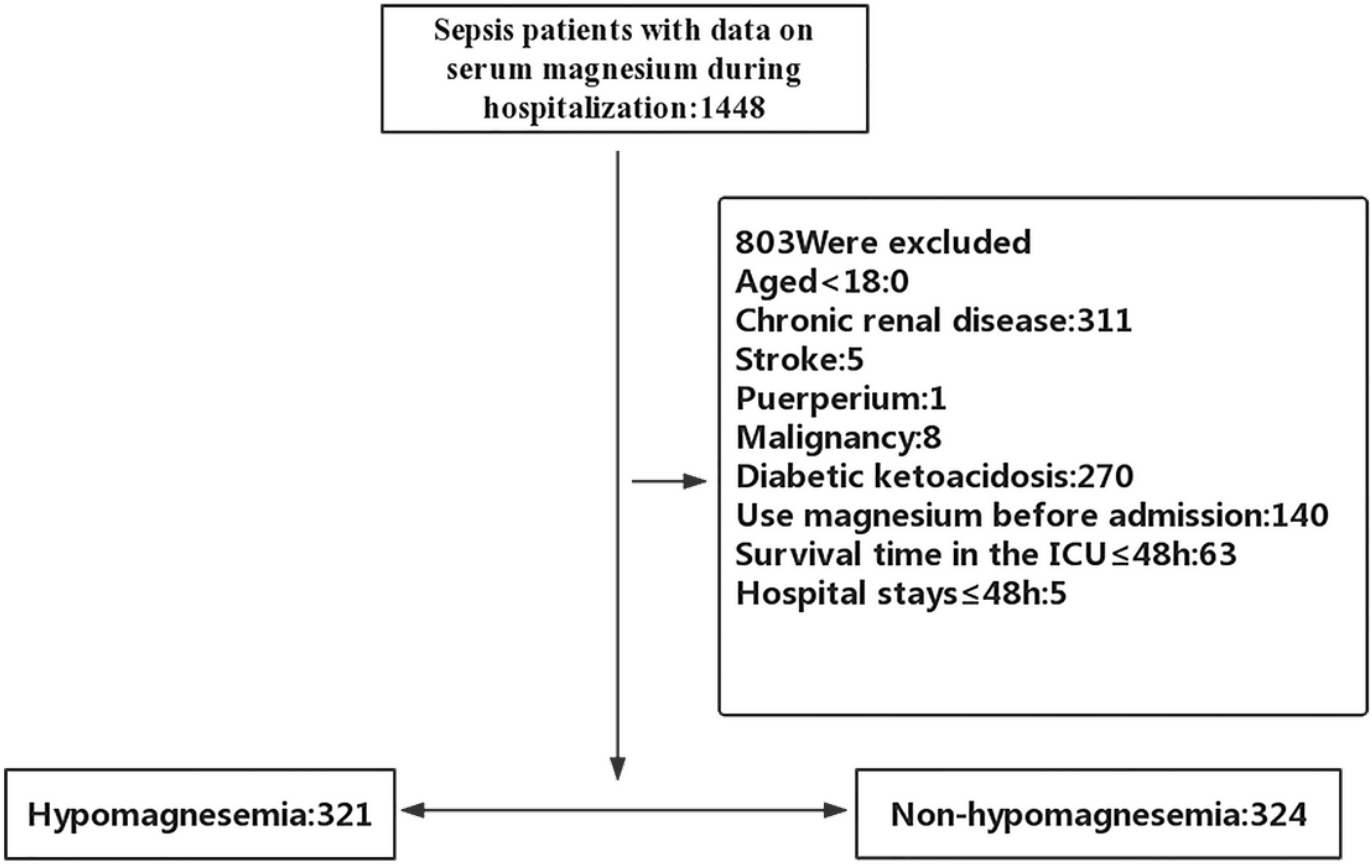

Figure 1

Exclusion criteria were as follows: patients with chronic kidney disease, cerebrovascular accident, malignant tumor, or diabetic ketoacidosis (DKA), puerperal women, under the age of 18, use of magnesium supplements prior to admission. (Figure 1)

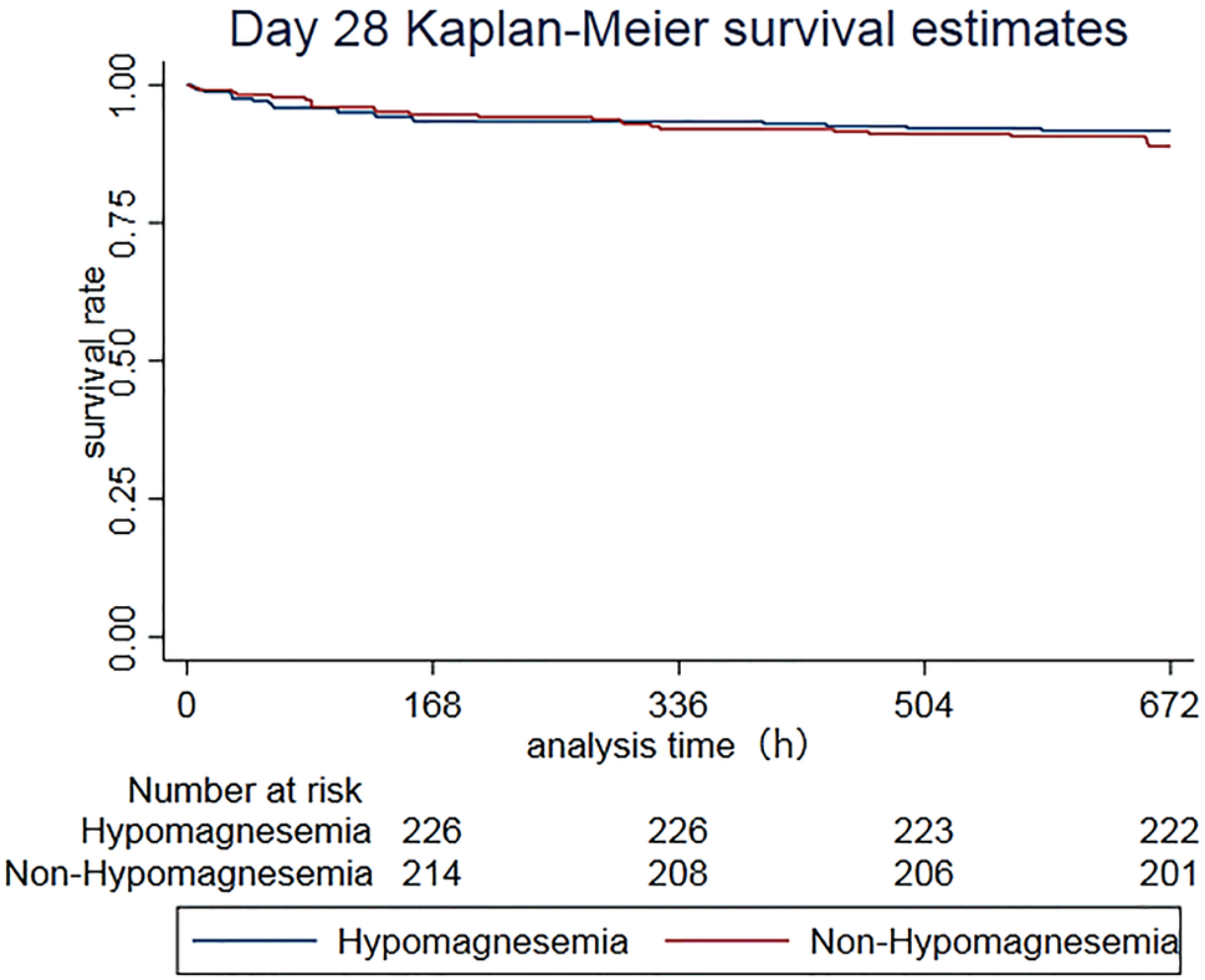

Figure 2

K-M curve shows the number of patients who survived at 7/14/21/28 days after discharge from the hospital in the two groups (Figure 2).

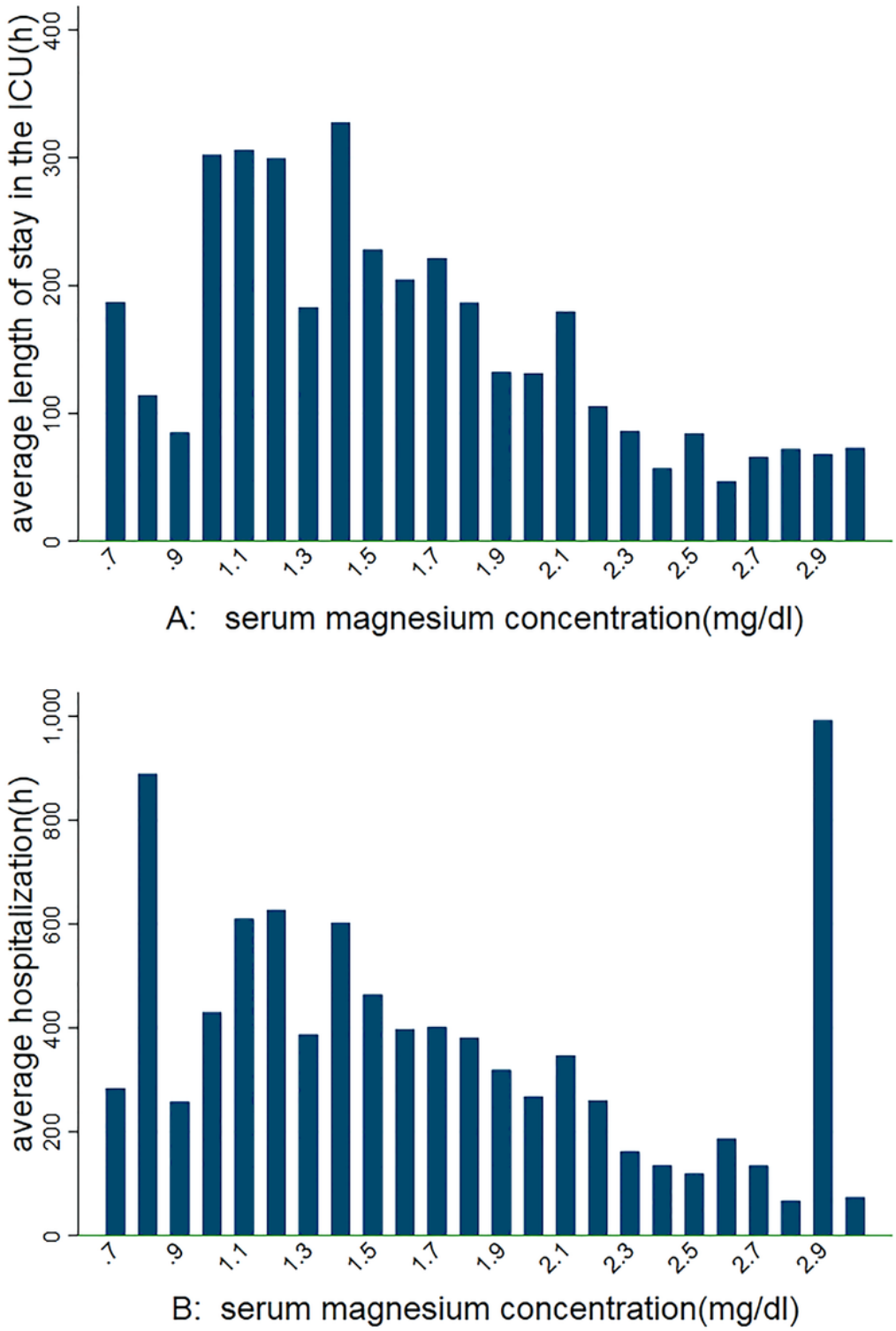

Figure 3

We made histograms of the average ICU time (Figure A) and average hospital stay (Figure B) for different magnesium levels (Figure 3).

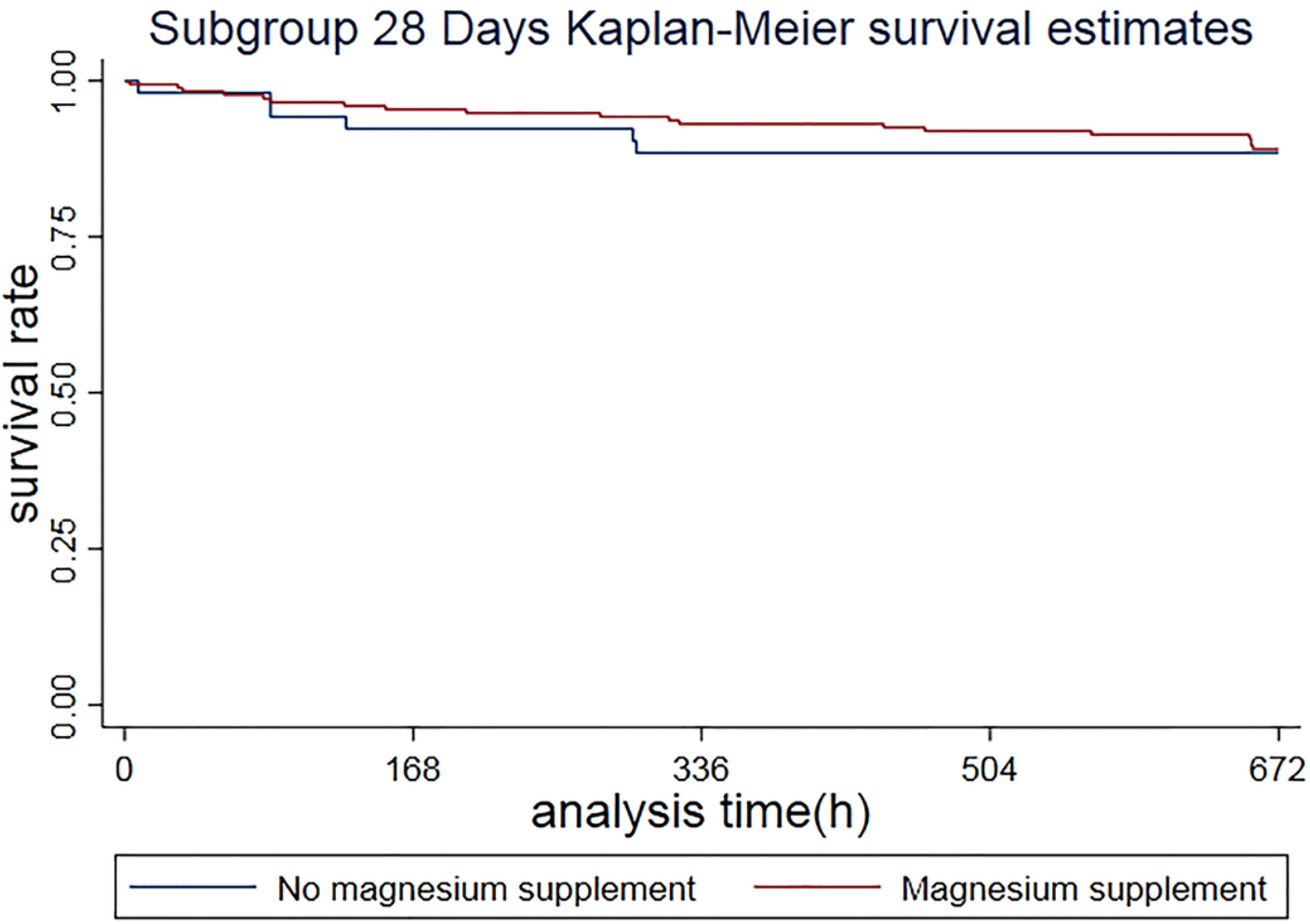

Figure 4

In addition, the 14-day mortality (P < 0.01) and 28-day mortality (P = 0.03) of patients in group B were significantly lower than those in group A (Figure 4).