Association between serum magnesium trajectory and in-hospital mortality in hospitalized patients with sepsis: an analysis of the MIMIC-IV database

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Abstract. Background: This study aimed to investigate the association between serum magnesium trajectory and risk of in-hospital mortality in intensive care unit (ICU) patients with sepsis. Methods: Adult sepsis patients who had complete data on serum magnesium at ICU admission (at 0, 12, 24, 36 and 48 hours after ICU admission) based the 2012-2019 Medical Information Mart for Intensive Care IV (MIMIC-IV) database were included in this retrospective cohort study. Serum magnesium trajectories were identified using K-means cluster analysis. The multivariable Cox proportional-hazards model was used to evaluate the association between magnesium level at different time points or magnesium trajectory and in-hospital mortality. Results: A total of 2,270 patients with sepsis were enrolled, and in-hospital mortality occurred in 716 (31.54%). Three trajectories were identified: a high-level declining trajectory, normal-level stable trajectory, and low-level rising trajectory. Among the magnesium levels at different time points, a higher serum magnesium level only at ICU admission (0h) (hazard ratio [HR] = 1.13, 95% confidence interval [CI]: 1.03-1.23) was associated with an increased risk of in-hospital mortality. Compared with the normal-level stable trajectory group, patients in the low-level rising trajectory group (HR = 0.82, 95%CI: 0.70-0.97) had a reduced risk of in-hospital mortality, but no association with in-hospital mortality was found in patients in the high-level declining trajectory group (p=0.812). Conclusion: Sepsis patients with a low-level, rising magnesium trajectory may have a reduced risk of in-hospital mortality.

Key words: Sepsis; in-hospital mortality; magnesium levels; trajectory; intensive care units

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Sepsis is a life-threatening systemic inflammatory response syndrome caused by a dysregulated host response to infection, ultimately leading to septic shock and multi-organ failure [1, 2]. Sepsis is a common disease in intensive care units (ICUs), and its associated high mortality, morbidity, and enormous economic burden make it a global public health problem [3, 4]. In 2017, there were an estimated 48.9 million sepsis cases and 11.0 million sepsis-related deaths worldwide (19.7% of all global deaths) [5]. A meta-analysis reported that the estimated global incidence of ICU-treated sepsis was 58 per 100,000 person-years, two-fifths of whom died during hospitalization [6]. Therefore, the identification of death-related indicators in sepsis patients is important for timely intervention and improved prognosis of sepsis.

Serum magnesium testing is part of routine biochemical tests. Magnesium (Mg^{2+}) is one of the main cations in the human body, a cofactor that promotes more than 300 enzymatic reactions and plays a vital role in physiological processes, such as muscle and nerve function, heart rhythm, protein synthesis, and energy metabolism [7, 8]. Several bodies of evidence suggest that serum magnesium levels are associated with poor outcomes in patients with acute kidney injury, heart disease and other critical illnesses [9-11]. Wang *et al.* proposed that hypermagnesemia may be correlated with a higher risk of in-hospital mortality in children with sepsis in the ICU [12]. Tonai *et al*. reported that hypomagnesemia may be related to an increased risk of disseminated intravascular coagulation in adult ICU patients with sepsis [13]. A randomized controlled trial of patients with severe sepsis showed that maintaining serum magnesium levels at around 3 mg/dL with intravenous magnesium sulphate increased lactate clearance and shortened the length of stay in the ICU [14]. In previous studies, serum magnesium levels were generally based on measurements taken at a single time point (*e.g*., at admission), but electrolyte levels in hospitalized patients are constantly changing. Several studies have found an association between dynamically changing serum sodium levels and death in hospitalized patients [15, 16]. However, little is known about the relationship between the dynamics of magnesium levels during hospitalization and the outcomes of patients with sepsis. Thus, this study aimed to identify changes in serum magnesium level in ICU patients with sepsis and assess the possible association between these changes and in-hospital mortality.

Methods

Data source and study population

The data used in this retrospective cohort study were obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 1.0) database between 2012 and 2019. MIMIC-IV is a large, single-centre, open-access database of patients admitted to the ICU at the Beth Israel Deaconess Medical Center from 2008 to 2019, which includes demographic information, vital signs, laboratory testing, procedures, medications, caregiver notes, imaging reports, and mortality [17]. After completing an online course from the National Institutes of Health and passing an exam on the Protecting Human Study Participants, the author of this study was qualified to use the MIMIC-IV database. The included population should meet the following criteria: (1) adult patients (age ≥18 years old); (2) a diagnosis of sepsis; and (3) ICU stay ≥48 hours. Patients were excluded if they met the following criteria: (1) serum magnesium measurements taken less than five times within 48 hours after ICU admission; (2) missing information on mortality; and (3) death within 48 hours after ICU admission. Sepsis was diagnosed according to the Sepsis 3.0 criteria; sepsis was defined as a documented or suspected infection plus an acute change in total Sequential Organ Failure Assessment (SOFA) of ≥2 points [18]. Infection was identified from the International Classification of Diseases (ICD-9) code. The MIMIC-IV was approved by the institutional review boards of Beth Israel Deaconess Medical Center (Boston, MA, USA) and Massachusetts Institute of Technology (Cambridge, MA, USA). Informed consent was not required because information related to patients' identities was re-coded and identifiable information was hidden.

Outcome

The outcome of this study was in-hospital mortality, defined as the survival status at hospital discharge. The follow-up period was

from the time of patient admission to the time of patient discharge or death. For patients with multiple hospital admissions, only data from the patient's first ICU admission were used. All included patients had five measurements of serum magnesium levels taken within 48 hours of admission to the ICU, with the first measurement at the time of admission to the ICU (0 hours) and subsequent measurements at 12-hour intervals (at 12, 24, 36, and 48 hours).

Variables

Data were extracted from the MIMIC-IV database through the Structured Query Language. Baseline characteristics of patients' first admission and laboratory measurements taken within 48 hours after ICU admission were collected. These variables included: age, sex (male, female), race (white, black, others), insurance (Medicaid, Medicare, others), marital status (married, others), use of mechanical ventilation (yes, no), use of vasopressor (yes, no), acute kidney injury (AKI, yes, no), respiratory failure (yes, no), cardiogenic shock (yes, no), magnesium sulphate (yes, no), 48-hour urine output (mL), length of ICU stay (day), heart rate (b.p.m.), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), respiratory rate (times per minute), temperature (°C), percutaneous arterial oxygen saturation (SpO_2, %), Glasgow Coma Scale (GCS, score), Charlson comorbidity index (score), SOFA (score), Simplified Acute Physiology Score II (SAPS II, score), Systemic Inflammatory Response Syndrome (SIRS, score), white blood cells (10^9/L), platelet (10^9/L), haemoglobin (g/dL), lactate (mmol/L), red blood cell distribution width (%), serum creatinine (mg/dL), international normalized ration, prothrombin time (seconds), partial thromboplastin time (seconds), blood urea nitrogen (g/dL), glucose (mg/dL), pH, sodium (mEq/L), potassium (mEq/L), chloride (mEq/L), bicarbonate (mEq/L), arterial partial pressure of oxygen (PaO_2, mmHg), arterial partial pressure carbon dioxide ($PaCO_2$, mmHg), magnesium levels (mg/dL), and follow-up time (days). AKI was determined based on the Kidney Disease Improving Global Outcomes (KDIGO) consensus criterion of a >50% increase in serum creatinine concentration from the baseline creatinine concentration, measured within three months before enrolment [19].

Statistical analysis

Continuous data were expressed as mean and standard deviation (mean ± SD) or median and quartiles (M [Q1, Q3]). The t-test was used to compare normally distributed continuous data and the Wilcoxon signed-rank test was used for non-normally distributed continuous data. Categorical data were reported using numbers and percentages (*n* [%]), and the Chi-square test was used to compare differences between groups. Characteristics were compared between patients who died and those who survived.

For some of the covariates, there were missing values, and the covariate with the largest amount of missing values was lactate with 8.81% missing values. Missing values of covariates were interpolated using random forest imputation. Sensitivity analysis was performed before and after the imputation of missing data. The univariable Cox proportional-hazards model was used to screen covariates, and covariates with $p<0.05$ were included in the multivariable Cox proportional-hazards model, and least absolute shrinkage and selection operator (LASSO) regression was utilized to determine adjusted covariates. After the screening, covariates containing age, use of mechanical ventilation, use of vasopressor, AKI, respiratory failure, cardiogenic shock, 48-hour urine output, length of ICU stay, temperature, Charlson comorbidity index, SOFA, SAPS II, red blood cell distribution width, partial thromboplastin time, blood urea nitrogen, PaO_2, and lactate were adjusted in the multivariable Cox proportional-hazards model (*supplementary table 1*). Serum magnesium trajectories were identified using K-means cluster analysis based on five serum magnesium measurements taken within 48 hours of the patient's ICU admission. K-means cluster analysis is a type of unsupervised machine learning that groups unlabelled datasets into different clusters by features. The multivariable Cox proportional-hazards model was used to evaluate the association between a single serum magnesium level (at 0, 12, 24, 36 and 48 hours) or serum magnesium trajectory and in-hospital mortality in patients with sepsis, reported as hazard ratio (HR) with a 95% confidence interval (CI). Statistical analyses were performed using SAS 9.4 software

(SAS Institute Inc., Cary, NC, USA) and R software (version 4.2.1). A two-sided p value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 7,495 patients with sepsis were recorded in the MIMIC-IV database from 2012 to 2019. Twenty-seven patients who were admitted to the ICU for less than 48 hours and 5,198 patients with incomplete data based on five serum magnesium measurements were excluded. Finally, 2,270 patients with sepsis were enrolled (*figure 1*). The characteristics of patients are presented in *table 1*. Of these patients, in-hospital mortality occurred in 716 (31.54%) patients and 1,554 (68.46%) patients survived at discharge. The mean age ± SD of patients was 61.60 ± 16.00 years, 58.24% (1,322 cases) were male, and 58.06% (1,318 cases) were white. The median (quartiles) length of ICU stay was 10.30 (6.86, 15.95) days. The median (quartiles) SOFA score of patients was 10.00 (7.00, 13.00). The mean serum magnesium level ± SD at the time of ICU admission was 2.02 ± 0.59 mg/dL.

Serum magnesium levels at different time points and in-hospital mortality

The association between serum magnesium levels at different time points within 48 hours after admission to the ICU and in-hospital mortality is shown in *table 2*. Higher serum magnesium levels at ICU admission (HR=1.22, 95% CI: 1.13-1.32) were linked to an increased risk of in-hospital mortality in patients with sepsis, whereas there was no relationship between serum magnesium levels at 12, 24, 36, and 48 hours after ICU admission and in-hospital mortality (p>0.05). The multivariable Cox proportional-hazards model showed that higher serum magnesium levels only at ICU admission (HR=1.13, 95%CI: 1.03-1.23) were associated with an increased risk of in-hospital mortality in patients with sepsis. The association between serum magnesium levels at ICU admission and in-hospital mortality is presented in *figure 2*. The risk of in-hospital mortality in patients with

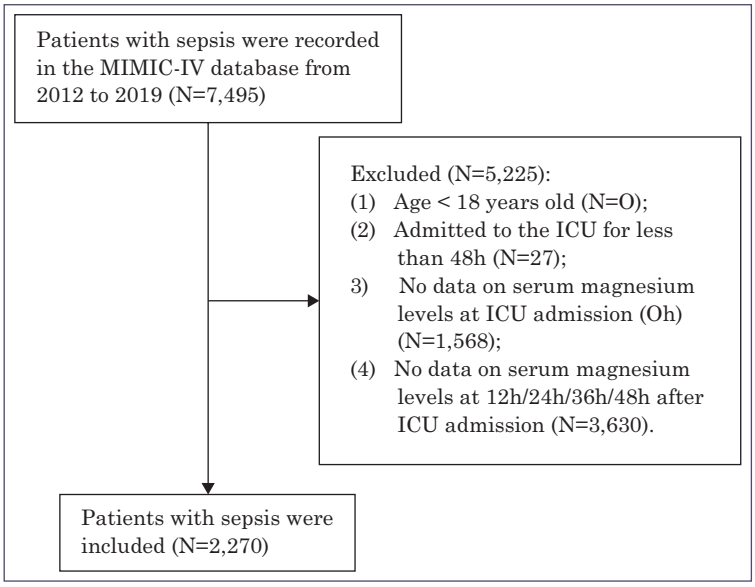

Figure 1. Flow chart of the study population. MIMIC-IV: the Medical Information Mart for Intensive Care IV; ICU: intensive care unit.

Table 1. Characteristics of patients with sepsis.

Variables	Total (n=2270)	Survivors (n = 1554)	In-hospital mortality (n = 716)	p
Age, years, mean ± SD	61.60 ± 16.00	60.02 ± 16.18	65.01 ± 15.05	<0.001
Sex, n (%)				0.715
Female	948 (41.76)	645 (41.51)	303 (42.32)	
Male	1322 (58.24)	909 (58.49)	413 (57.68)	
Race, n (%)				0.585
White	1318 (58.06)	913 (58.75)	405 (56.56)	
Black	174 (7.67)	119 (7.66)	55 (7.68)	
Other	778 (34.27)	522 (33.59)	256 (35.75)	
Insurance, n (%)				<0.001
Medicaid	199 (8.77)	142 (9.14)	57 (7.96)	
Medicare	980 (43.17)	629 (40.48)	351 (49.02)	
Other	1091 (48.06)	783 (50.39)	308 (43.02)	
Marital status, n (%)				0.867
Married	939 (41.37)	641 (41.25)	298 (41.62)	
Others	1331 (58.63)	913 (58.75)	418 (58.38)	
Mechanical ventilation, n (%)				0.003
No	30 (1.32)	28 (1.80)	2 (0.28)	
Yes	2240 (98.68)	1526 (98.20)	714 (99.72)	
Vasopressor, n (%)				<0.001
No	415 (18.28)	353 (22.72)	62 (8.66)	
Yes	1855 (81.72)	1201 (77.28)	654 (91.34)	
Acute kidney injury, n (%)				0.002
No	207 (9.12)	161 (10.36)	46 (6.42)	
Yes	2063 (90.88)	1393 (89.64)	670 (93.58)	
Respiratory failure, n (%)				<0.001
No	748 (32.95)	570 (36.68)	178 (24.86)	
Yes	1522 (67.05)	984 (63.32)	538 (75.14)	
Cardiogenic shock, n (%)				<0.001
No	1927 (84.89)	1354 (87.13)	573 (80.03)	
Yes	343 (15.11)	200 (12.87)	143 (19.97)	
Magnesium sulphate, n (%)				<0.001
No	860 (37.89)	547 (35.20)	313 (43.72)	
Yes	1410 (62.11)	1007 (64.80)	403 (56.28)	
48-h urine output, mL, M (Q_1, Q_3)	2691.50 (1273.00,4520.00)	2979.50 (1498.00,4855.00)	2055.00 (845.50,3855.00)	<0.001
Length of ICU stay, day, M (Q_1, Q_3)	10.30 (6.86,15.95)	10.44 (6.91,16.28)	10.03 (6.75,15.45)	0.074

Variables	Total (n=2270)	Survivors (n = 1554)	In-hospital mortality (n = 716)	p
Heart rate, b.p.m, mean ± SD	95.69 ± 22.51	95.61 ± 22.77	95.85 ± 21.95	0.817
SBP, mmHg, mean ± SD	118.56 ± 25.39	119.22 ± 25.38	117.12 ± 25.37	0.068
DBP, mmHg, mean ± SD	66.71 ± 19.43	67.14 ± 19.05	65.77 ± 20.21	0.119
Respiratory rate, times per minute, Mean ± SD	21.30 ± 6.85	21.19 ± 6.78	21.53 ± 7.00	0.271
Temperature, °C, mean ± SD	36.64 ± 1.13	36.72 ± 1.12	36.48 ± 1.14	<0.001
SPO_2, %, mean ± SD	96.21 ± 5.23	96.31 ± 5.24	96.00 ± 5.20	0.195
GCS, score, mean ± SD	13.28 ± 3.37	13.33 ± 3.33	13.15 ± 3.44	0.227
Charlson comorbidity index, score, M (Q_1, Q_3)	3.00 (2.00,5.00)	3.00 (1.00,5.00)	4.00 (2.00,6.00)	<0.001
SOFA, score, M (Q_1, Q_3)	10.00 (7.00,13.00)	10.00 (7.00,13.00)	11.00 (8.00,14.00)	<0.001
SAPS II, score, M (Q_1, Q_3)	47.00 (36.00,57.00)	45.00 (35.00,55.00)	50.00 (40.00,60.00)	<0.001
SIRS, score, mean ± SD	3.07 ± 0.82	3.06 ± 0.83	3.09 ± 0.81	0.493
White blood cells, 10^9/L, M (Q_1, Q_3)	12.60 (8.20,18.20)	12.40 (8.00,17.70)	13.50 (8.70,18.80)	0.011
Platelet, 10^9/L, M (Q_1, Q_3)	177.50 (112.00,256.00)	182.00 (119.00,259.00)	165.00 (98.00,245.00)	<0.001
Haemoglobin, g/dL, mean ± SD	10.55 ± 2.54	10.68 ± 2.54	10.26 ± 2.50	<0.001
Lactate, mmol/L, M (Q_1, Q_3)	2.40 (1.50,3.90)	2.30 (1.50,3.70)	2.60 (1.60,4.40)	<0.001
Red blood cell distribution width, %, mean ± SD	15.88 ± 2.70	15.64 ± 2.60	16.42 ± 2.85	<0.001
Serum creatinine, mg/dL, M (Q_1, Q_3)	1.40 (0.90,2.40)	1.40 (0.90,2.40)	1.55 (1.00,2.60)	0.009
International normalized ratio, ratio, M (Q_1, Q_3)	1.40 (1.20,1.90)	1.40 (1.20,1.80)	1.50 (1.20,2.20)	<0.001
Prothrombin time, second, M (Q_1, Q_3)	15.50 (13.20,20.50)	15.20 (13.10,19.40)	16.60 (13.55,23.50)	<0.001
Partial thromboplastin time, second, M (Q_1, Q_3)	34.10 (28.70,46.60)	33.25 (28.30,44.10)	36.65 (29.60,52.35)	<0.001
Blood urea nitrogen, g/dL, M (Q_1, Q_3)	29.00 (18.00,49.00)	27.00 (17.00,47.00)	32.00 (19.00,54.00)	<0.001
Glucose, mg/dL, M (Q_1, Q_3)	147.00 (112.00,200.00)	145.50 (112.00,197.00)	148.50 (114.50,206.00)	0.163
pH, mean ± SD	7.31 ± 0.12	7.31 ± 0.12	7.31 ± 0.12	0.916
Sodium, mEq/L, mean ± SD	137.61 ± 6.64	137.52 ± 6.58	137.79 ± 6.75	0.364
Potassium, mEq/L, mean ± SD	4.34 ± 0.95	4.34 ± 0.95	4.36 ± 0.93	0.554
Chloride, mEq/L, mean ± SD	103.17 ± 8.05	103.38 ± 8.01	102.71 ± 8.11	0.064
Bicarbonate, mEq/L, mean ± SD	20.47 ± 5.68	20.60 ± 5.69	20.21 ± 5.63	0.127
PaO_2, mmHg, M (Q_1, Q_3)	108.00 (74.00,185.00)	111.00 (76.00,189.00)	100.00 (70.00,175.00)	0.005

Variables	Total (n=2270)	Survivors (n = 1554)	In-hospital mortality (n = 716)	p
$PaCO_2$, mmHg, mean ± SD	41.73 ± 13.47	42.10 ± 13.66	40.94 ± 13.04	0.056
Magnesium at 0h, mg/dL, mean ± SD	2.02 ± 0.59	1.98 ± 0.52	2.12 ± 0.71	<0.001
Magnesium at 12h, mg/dL, mean ± SD	2.16 ± 0.72	2.14 ± 0.71	2.19 ± 0.74	0.161
Magnesium at 24h, mg/dL, mean ± SD	2.15 ± 0.40	2.14 ± 0.41	2.16 ± 0.35	0.401
Magnesium at 36h, mg/dL, mean ± SD	2.14 ± 0.37	2.14 ± 0.38	2.15 ± 0.34	0.893
Magnesium at 48h, mg/dL, mean ± SD	2.14 ± 0.36	2.13 ± 0.37	2.14 ± 0.32	0.594
Follow-up time, days, M (Q_1, Q_3)	17.28 (11.13,26.55)	19.73 (13.56,29.82)	11.98 (7.46,18.34)	<0.001

ICU: intensive care unit; SBP: systolic blood pressure; DBP: diastolic blood pressure; SPO2: percutaneous arterial oxygen saturation; GCS: Glasgow Coma Scale; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score II; SIRS: Systemic Inflammatory Response Syndrome; PaO2: arterial partial pressure of oxygen; PaCO2: arterial partial pressure carbon dioxide.

Table 2. Association between serum magnesium levels at different time points within 48 hours after ICU admission and in-hospital mortality.

Serum magnesium levels at different time points	Univariable model		Multivariable model	
	HR (95% CI)	p	HR (95% CI)	p
0 h	1.22 (1.13-1.32)	<0.001	1.13 (1.03-1.23)	0.007
12 h	1.06 (0.98-1.14)	0.12	0.97 (0.90-1.05)	0.461
24 h	1.10 (0.94-1.29)	0.214	0.99 (0.82-1.20)	0.93
36 h	1.05 (0.87-1.26)	0.612	0.92 (0.74-1.14)	0.452
48 h	1.10 (0.91-1.33)	0.334	1.03 (0.83-1.28)	0.779

ICU: intensive care unit; HR: hazard ratio; CI: confidence interval.
Multivariable model adjusted for age, mechanical ventilation, vasopressor use, AKI, respiratory failure, cardiogenic shock, 48-hour urine output, length of ICU stay, temperature, Charlson comorbidity index, SOFA, SAPS II, red blood cell distribution width, partial thromboplastin time, blood urea nitrogen, PaO2, and lactate.

sepsis increased with elevated serum magnesium levels at ICU admission.

Serum magnesium trajectories and in-hospital mortality

Serum magnesium levels in sepsis patients admitted to the ICU for 48 hours were divided into three trajectories by K-means cluster analysis (*figure 3*). These three trajectories were a high-level declining trajectory, normal-level stable trajectory, and low-level rising trajectory. The characteristics of three serum magnesium trajectories are presented in *table 3*. The serum magnesium level in the low-level rising trajectory group was 1.70 ± 0.29 mg/dL at ICU admission and 1.97 ± 0.24 mg/dL at 48 hours after ICU admission. The serum magnesium level in the normal-level stable trajectory was 2.15 ± 0.34 mg/dL at ICU admission and 2.20 ± 0.29 mg/dL at 48 hours after ICU admission. The serum magnesium level in the high-level declining trajectory group was 3.10 ± 1.27 mg/dL at ICU admission and 2.65 ± 0.61 mg/dL at 48 hours after ICU admission. The distribution of serum magnesium levels in the three trajectory groups is presented in *supplementary figure 1*.

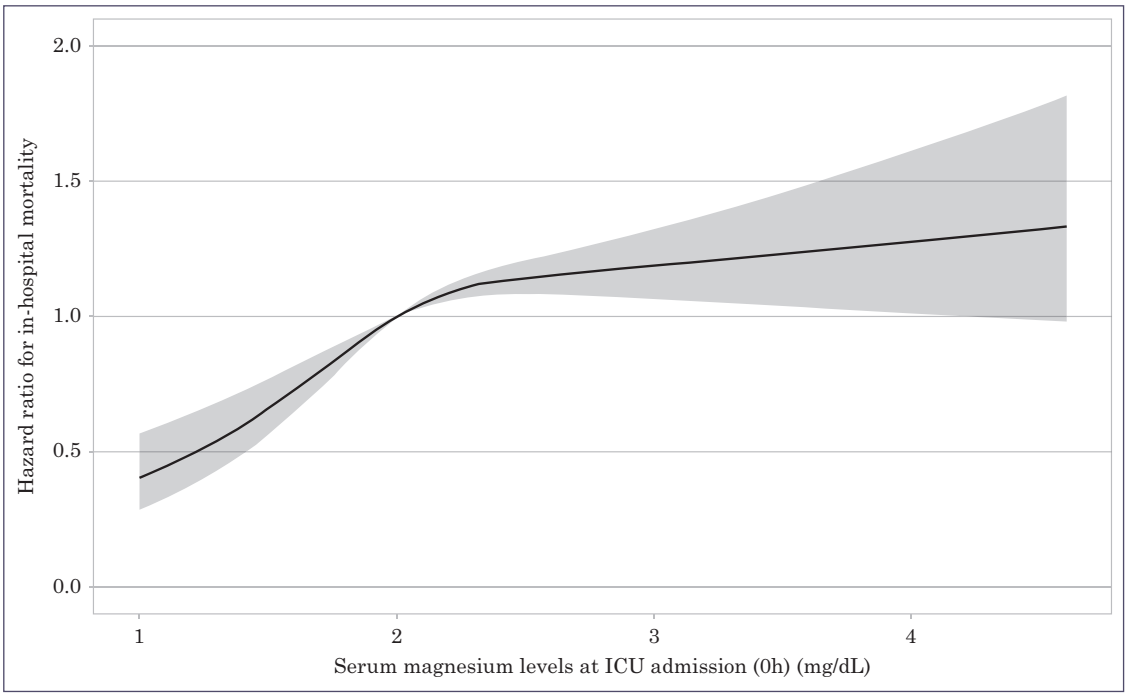

Figure 2. Restricted cubic spline (RCS) model showing the association between serum magnesium levels at ICU admission (0 hours) and in-hospital mortality in patients with sepsis. ICU: intensive care units.

Compared with the normal-level stable trajectory group, patients in the low-level rising trajectory group (HR=0.69, 95% CI: 0.59-0.81) had a reduced risk of in-hospital mortality, but no association with in-hospital mortality was found for patients in the high-level declining trajectory group (p=0.64) (*table 4*). The multivariable Cox proportional-hazards model adjusted for covariates demonstrated that patients in the low-level rising trajectory group (HR=0.82, 95% CI: 0.70-0.97) still had a reduced risk of in-hospital mortality.

Discussion

The relationship between serum magnesium trajectories within 48 hours after ICU admission and in-hospital mortality in patients with sepsis was analysed. Serum magnesium trajectories reflect the dynamic change in magnesium level in patients over time. In this study, serum magnesium levels in sepsis patients admitted to the ICU for 48 hours were divided into three trajectories: a high-level declining trajectory, normal-level stable trajectory, and low-level rising trajectory. The results demonstrated that sepsis patients in the low-level rising trajectory group had a reduced risk of in-hospital mortality compared with those in the normal-level stable trajectory group.

Magnesium acts as a cofactor in many enzymatic reactions and is involved in the biochemical processes of oxidative metabolism, protein and nucleic acid synthesis, and immune responses [8, 20, 21]. Based on previous studies, it has been proposed that magnesium is related to dysregu-

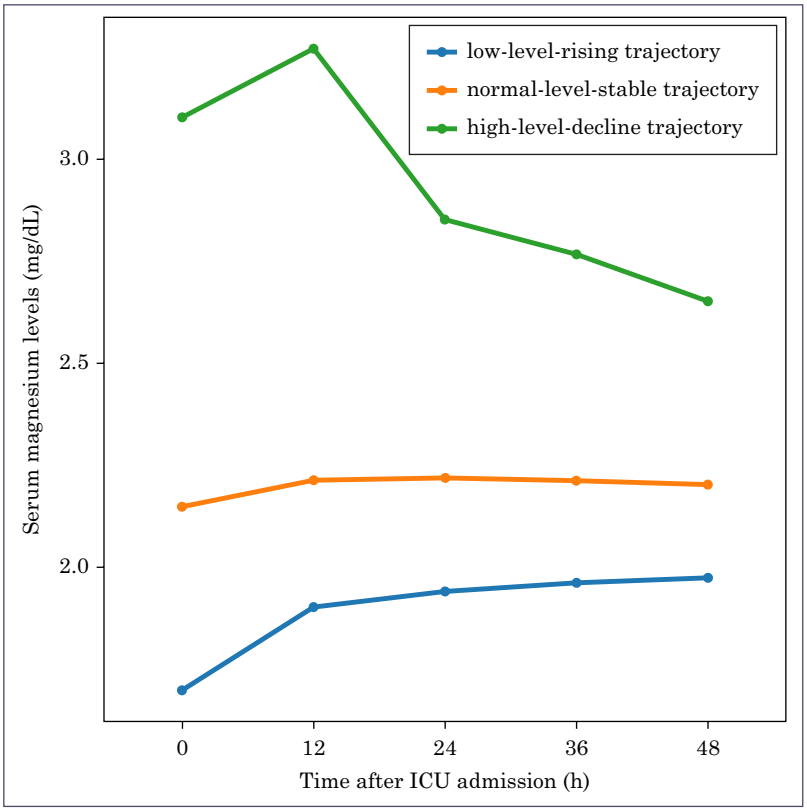

Figure 3. Serum magnesium trajectories in ICU-admitted sepsis patients identified by K-means cluster analysis.

lation of the host response to infection and the pathophysiology of sepsis [22, 23]. Both high and low serum magnesium levels have been reported to be associated with poor prognosis in ICU patients [9, 10, 12]. A systematic review and meta-analysis found that hypomagnesemia was related to a higher risk of mortality, sepsis, mechanical ventilation, and the length of ICU stay in ICU patients [10]. Wang *et al.* reported that hypomagnesemia is a risk factor associated with in-hospital mortality in children with sepsis [12]. The previous analyses were reported based on a single serum magnesium level at the time of patient admission. However, in the current study, we analysed the relationship between serum magnesium levels at different time points during 48 hours of ICU admission and in-hospital mortality in patients with sepsis. Our results reveal that higher serum magnesium levels only at ICU admission (0 hours) correlated with an increased risk of in-hospital mortality. A possible explanation is that measurement at the time of initial ICU admission reflects the patient's true serum magnesium level, while interventions after ICU admission may affect the patient's serum magnesium level.

Serum magnesium levels measured at a single time point do not appear to reflect an association between dynamic changes in serum magnesium level and in-hospital mortality. Several studies have demonstrated the impact of dynamic changes in indicators (trajectories) on the outcome of patients [16, 24-26]. Chewcharat *et al.* indicated that trajectories of serum sodium levels in hospitalized patients were significantly associated with one-year

Table 3. Characteristics of the three serum magnesium trajectories.

Serum magnesium levels	Low-level rising trajectory	Normal-level stable trajectory	High-level declining trajectory	*p*
0 h, mg/dL, mean ± SD	1.70 ± 0.29	2.15 ± 0.34	3.10 ± 1.27	<0.001
12 h, mg/dL, mean ± SD	1.90 ± 0.30	2.21 ± 0.31	3.27 ± 2.09	<0.001
24 h, mg/dL, mean ± SD	1.94 ± 0.24	2.22 ± 0.28	2.85 ± 0.71	<0.001
36 h, mg/dL, mean ± SD	1.96 ± 0.23	2.21 ± 0.27	2.77 ± 0.66	<0.001
48 h, mg/dL, mean ± SD	1.97 ± 0.24	2.20 ± 0.29	2.65 ± 0.61	<0.001

Table 4. Association between serum magnesium trajectories within 48 hours after ICU admission and in-hospital mortality.

Serum magnesium trajectories	Univariable model		Univariable model	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Normal-level stable trajectory	Ref		Ref	
Low-level rising trajectory	0.69 (0.59-0.81)	<0.001	0.82 (0.70-0.97)	0.019
High-level declining trajectory	1.07 (0.81-1.41)	0.640	0.97 (0.73-1.28)	0.812

ICU: intensive care unit; HR: hazard ratio; CI: confidence interval; Ref: reference.
Multivariable model adjusted for age, mechanical ventilation, vasopressor use, AKI, respiratory failure, cardiogenic shock, 48-hour urine output, length of ICU stay, temperature, Charlson comorbidity index, SOFA, SAPS II, red blood cell distribution width, partial thromboplastin time, blood urea nitrogen, PaO_2, and lactate.

mortality [16]. We divided sepsis patients into three trajectory groups based on the changes in serum magnesium levels during 48 hours of their ICU admission. Our findings show that patients in the low-level rising trajectory group had a reduced risk of in-hospital mortality, but no association was found between a high-level declining trajectory and in-hospital mortality. For patients in the low-level rising trajectory group, the entire trajectory was within normal range, although the patients' serum magnesium levels on ICU admission were near the threshold for normal range at 1.70 ± 0.29 mg/dL. More studies are needed to confirm the association between low serum magnesium trajectories within normal range and the lower risk of in-hospital mortality in patients with sepsis. In patients with a high-level declining trajectory, the mean serum magnesium level at the time of ICU admission was higher, at 3.10 ± 1.27 mg/dL, but the magnesium level in this trajectory group showed a rapid decline, with the magnesium level dropping to 2.65 ± 0.61 mg/dL at 48 hours after ICU admission, still maintaining a decreasing trend. This may be the reason why there was no statistically significant difference in the association between in-hospital mortality and high-level declining trajectory or normal-level stable trajectory. Future studies are needed to explore the association between long-term serum magnesium trajectories and outcome in patients with sepsis.

In this study, we determined serum magnesium trajectories and further investigated whether these trajectories were associated with in-hospital mortality in ICU patients with sepsis. Our study may provide epidemiological evidence for changes in serum magnesium levels after ICU admission in patients with sepsis and their association with in-hospital mortality. However, there are several limitations to this study. First, this study was a retrospective cohort study, and therefore a causal association may not be inferred. Second, a large proportion of patients were excluded due to the absence of complete serum magnesium measurement data at the five

time points (0, 12, 24, 36, and 48 hours after ICU admission), which may have contributed to selection bias. Third, the current study would benefit from a group consisting of patients with longer-term serum magnesium measurements.

Conclusions

In this study, three trajectories of serum magnesium were characterised relative to in-hospital mortality in ICU patients with sepsis. The results show that sepsis patients in the low-level rising trajectory group had a reduced risk of in-hospital mortality. Further studies may need to focus on the association between long-term serum magnesium trajectory and outcome in patients with sepsis.

Disclosure

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References

1. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. *Bmj* 2016; 353: i1585.
2. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet* 2018; 392: 75-87.
3. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. *N Engl J Med* 2017; 377: 414-7.
4. Markwart R, Saito H, Harder T, *et al.* Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. *Intensive Care Med* 2020; 46: 1536-51.
5. Rudd KE, Johnson SC, Agesa KM, *et al.* Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; 395: 200-11.
6. Fleischmann-Struzek C, Mellhammar L, Rose N, *et al.* Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med* 2020; 46: 1552-62.
7. Buckley MS, Leblanc JM, Cawley MJ. Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. *Crit Care Med* 2010; 38: S253-264.
8. Noronha JL, Matuschak GM. Magnesium in critical illness: metabolism, assessment, and treatment. *Intensive Care Med* 2002; 28: 667-9.
9. Naksuk N, Hu T, Krittanawong C, *et al.* Association of Serum Magnesium on Mortality in Patients Admitted to the Intensive Cardiac Care Unit. *Am J Med* 2017; 130: 229.e225-229.e213.
10. 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* 2017; 47: 288-95.
11. Cheungpasitporn W, Thongprayoon C, Erickson SB. Admission hypomagnesemia and hypermagnesemia increase the risk of acute kidney injury. *Ren Fail* 2015; 37: 1175-9.
12. Wang H, Huang J, Jin X, *et al.* Hypermagnesaemia, but Not Hypomagnesaemia, Is a Predictor of Inpatient Mortality in Critically Ill Children with Sepsis. *Dis Markers* 2022; 2022: 3893653.
13. Tonai K, Katayama S, Koyama K, *et al.* Association between hypomagnesemia and coagulopathy in sepsis: a retrospective observational study. *BMC Anesthesiol* 2022; 22: 359.
14. 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* 2020; 76: 175-84.
15. Lin Z, Zheng J, Liu X, Hu X, Fuxian R, Gao D. Assessing potassium levels in critically ill patients with heart failure: application of a group-based trajectory model. *ESC Heart Fail* 2023; 10: 57-65.
16. Chewcharat A, Thongprayoon C, Cheungpasitporn W, Mao MA, Thirunavukkarasu S, Kashani KB. Trajectories of Serum Sodium on In-Hospital and 1-Year Survival among Hospitalized Patients. *Clin J Am Soc Nephrol* 2020; 15: 600-7.
17. Johnson, A., Bulgarelli, L., Pollard, T., Horng, S., Celi, L. A., & Mark, R. (2021). MIMIC-IV (version 1.0). PhysioNet. 2021. https://doi.org/10.13026/s6n6-xd98. Accessed April 20, 2023.
18. Singer M, Deutschman CS, Seymour CW, *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* 2016; 315: 801-10.
19. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; 158: 825-30.

20. Pickering G, Mazur A, Trousselard M, *et al.* Magnesium Status and Stress: The Vicious Circle Concept Revisited. *Nutrients* 2020; 12.

21. Gu Y, Tang J, Zhang F, *et al.* Manganese potentiates lipopolysaccharide-induced innate immune responses and septic shock. *Int J Biol Macromol* 2023; 230: 123202.

22. Chaigne-Delalande B, Lenardo MJ. Divalent cation signaling in immune cells. *Trends Immunol* 2014; 35: 332-344.

23. Wang D, Zheng J, Hu Q, *et al.* Magnesium protects against sepsis by blocking gasdermin D N-terminal-induced pyroptosis. *Cell Death Differ* 2020; 27: 466-81.

24. Pedersen M, Grindem H, Berg B, *et al.* Four Distinct 5-Year Trajectories of Knee Function Emerge in Patients Who Followed the Delaware-Oslo ACL Cohort Treatment Algorithm. *Am J Sports Med* 2022; 50: 2944-52.

25. Sun ZJ, Wang JW, Chang DY, *et al.* Unstably controlled systolic blood pressure trajectories are associated with markers for kidney damage in prediabetic population: results from the INDEED cohort study. *J Transl Med* 2020; 18: 194.

26. Liu T, Zhang Q, Song C, *et al.* C-reactive protein trajectories and the risk of all cancer types: A prospective cohort study. *Int J Cancer* 2022; 151: 297-307.