# The impact of magnesium sulfate administration on the prognosis of septic patients with hypomagnesemia: a retrospective propensity score-matched cohort study based on MIMIC-IV

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## Abstract

**Introduction:** This study aimed to provide a basis for optimizing clinical treatment by retrospectively analyzing the clinical characteristics of hypomagnesemia in sepsis patients and the impact of magnesium sulfate administration on their prognosis.

**Material and methods:** Based on inclusion and exclusion criteria, we included adult individuals diagnosed with sepsis and concurrent hypomagnesemia. Exposure was defined as administration of magnesium sulfate on the first day of ICU admission. The primary outcome assessed was the 28-day mortality rate. Secondary outcomes encompassed mortality rates at 90 and 365 days, the duration of mechanical ventilation, requirement for continuous renal replacement therapy (CRRT), hospital stay duration, intensive care unit (ICU) stay duration, hospital mortality, and ICU mortality. A multivariable Cox regression analysis was conducted to evaluate the relationship between sepsis with hypomagnesemia and 28-day mortality. Propensity score matching (PSM) was performed at a 1 : 1 ratio. Multivariable analysis was used to adjust for confounding factors.

**Results:** In the PSM analysis, the 28-day mortality rate appeared reduced in the magnesium sulfate treatment group relative to the untreated group (10.15% [33/3192] vs. 16.31% [53/347]). Magnesium sulfate use correlated with a decreased 28-day mortality rate (hazard ratio [HR] = 0.61; 95% CI: 0.39–0.94; $p$ = 0.026). Magnesium sulfate administration also reduced the 90-day mortality rate ($p$ = 0.039). Statistical analysis revealed no significant differences between magnesium sulfate administration and the use of CRRT, mechanical ventilation duration, hospital and ICU lengths of stay, or mortality rates at 365 days.

**Conclusions:** The administration of magnesium sulfate is associated with a reduced mortality rate in individuals diagnosed with sepsis and hypomagnesemia, providing theoretical support for clinical practice.

**Key words:** hypomagnesemia, sepsis, magnesium sulfate, mortality, MIMIC-IV.

## Introduction

Sepsis is defined as a common critical condition in which a dysregulated host response to infection leads to life-threatening organ dys-

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function, posing a severe threat to patient survival [1, 2]. It is characterized by high incidence and mortality rates and remains one of the leading causes of death worldwide, severely endangering human health and increasing global economic and societal burdens [3–5]. An epidemiological study on sepsis published in *The Lancet* in 2020, which analyzed the global burden of disease from 1990 to 2017, indicated that sepsis may be the leading cause of death worldwide, with the most severe impact observed in low- and middle-income countries [6]. Critically ill patients often experience various severe electrolyte imbalances, particularly under the stress of sepsis, with the incidence of hypomagnesemia exceeding 65% in these patients [7, 8]. Given the high incidence of hypomagnesemia in septic patients, it is important to investigate whether magnesium supplementation can improve the prognosis of patients with sepsis and concurrent hypomagnesemia.

The mechanisms by which sepsis leads to hypomagnesemia are not yet fully understood. Possible factors include impaired intestinal function due to inflammatory responses, dilution of serum magnesium from fluid resuscitation, drug-induced inhibition of magnesium reabsorption, and the propensity of sepsis to cause metabolic acidosis. The acidic environment may promote the intracellular transfer of magnesium ions, while renal impairment can lead to reabsorption defects. Additionally, low protein levels can reduce the binding of magnesium ions to proteins, resulting in ion loss. All these pathophysiological changes can contribute to the development of hypomagnesemia [9–13]. Magnesium exists in ionic form in all cells of the human body, serving as an important cofactor for ATP and participating in physiological processes by binding to nucleotides and regulating enzyme activity, making it an essential cation for human health [13]. Severe magnesium deficiency can lead to a range of health issues, including migraines, Alzheimer's disease, cerebrovascular accidents (strokes), hypertension, cardiovascular diseases, type 2 diabetes, seizures, coma, and even death [7, 14]. Meta-analyses of prospective studies have also indicated that patients with hypomagnesemia have a higher risk of cardiovascular diseases and poor prognosis [15]. Furthermore, studies have confirmed that, compared to patients with normal serum magnesium levels, critically ill patients with hypomagnesemia experience increased hospital mortality, longer ICU length of stay, and higher demand for mechanical ventilation [16].

Hypomagnesemia often coexists with other electrolyte imbalances, and clinical biochemical markers are usually delayed and not routinely monitored for serum magnesium levels. Consequently, magnesium ion levels are frequently overlooked by clinicians. However, magnesium supplementation is typically only considered by physicians when hypomagnesemia presents with significant clinical symptoms, leading to insufficient recognition and emphasis on the importance of hypomagnesemia and the necessity for its treatment [17]. As a result, the clinical practice of correcting hypomagnesemia with magnesium sulfate is not actively pursued. Moreover, it remains unclear whether magnesium supplementation can improve the prognosis of sepsis patients with hypomagnesemia or establish clinical treatment guidelines for hypomagnesemia [8, 18].

To enhance the awareness of healthcare professionals regarding hypomagnesemia in critically ill patients and to ensure timely treatment measures that can improve patient prognosis and establish treatment guidelines for patients with severe hypomagnesemia, we aimed to gather relevant evidence. To achieve this, we conducted a retrospective cohort study using the MIMIC-IV database to investigate the impact of magnesium sulfate use on the prognosis of sepsis patients with concurrent hypomagnesemia.

## Material and methods

### Data source

A retrospective cohort study utilizing propensity score matching was performed using the MIMIC-IV database. MIMIC-IV (version 2.2) is a publicly available, extensive medical database composed of five key components, with a primary emphasis on hospital and ICU-related data. The ICU section contains clinical data for more than 50,000 patients who were admitted to the ICU at Beth Israel Deaconess Medical Center between 2008 and 2019. To protect patient privacy, a random coding system is used to replace patient identities. Additionally, as MIMIC-IV is an open-source database, informed consent was obtained when patient data were collected prior to the establishment of the database. Therefore, we do not need to obtain further informed consent or ethical approval for this study. The first author of this study obtained access and usage rights to the database through systematic learning and theoretical examinations (ID: 12754211).

### Study population

Patients in this study were selected based on inclusion and exclusion criteria. The diagnosis of sepsis was based on the Third International Consensus Definitions for Sepsis and Septic Shock [1]. Hypomagnesemia is defined as a serum magnesium concentration of less than 1.7 mg/dl

(< 0.7 mmol/l), while the normal serum magnesium concentration for adults is between 1.7 and 2.4 mg/dl (0.7–1.0 mmol/l) [17]. Magnesium supplementation is defined as the administration of magnesium sulfate on the first day after ICU admission. Inclusion criteria: (1) Patients with a diagnosis of sepsis at the time of ICU admission were included; (2) first ICU admission; (3) complete clinical data. The exclusion criteria were as follows: (1) age < 18 years; (2) ICU stay < 24 h; (3) absence of magnesium monitoring upon ICU admission; (4) absence of magnesium monitoring on the fourth day of ICU stay; (5) patients with magnesium levels ≥ 1.7 mg/dl at the time of ICU admission; (6) patients with magnesium levels < 1.7 mg/dl on the fourth day.

### Exposure, grouping, and outcomes

Exposure is defined as receiving magnesium sulfate infusion on the first day of ICU admission, with magnesium levels remaining normal on the third day after supplementation, indicating that the infusion of magnesium sulfate has quantitatively and qualitatively reversed hypomagnesemia, thereby demonstrating treatment efficacy [17]. The study population was categorized into two groups: one that received magnesium sulfate infusion and another that did not. The primary outcome measure was the 28-day mortality rate. Secondary outcomes encompassed the mortality rates at 90 and 365 days, the duration of mechanical ventilation, the need for CRRT, hospital and ICU lengths of stay, as well as hospital and ICU mortality rates.

### Data extraction, collection, and management

Data extraction was carried out utilizing Structured Query Language (SQL). The SQL script was obtained from the following website: https://github.com/MIT-LCP/mimic-iv. Patient characteristics were collected, including demographics (age, gender, race, BMI), vital signs (heart rate, oxygen saturation, mean arterial pressure, respiratory rate, temperature), clinical treatments (CRRT, vasopressor medications, mechanical ventilation), relevant comorbidities (diabetes, hypertension, congestive heart failure, acute kidney injury, cancer), disease severity (ApsIII, OASIS, SOFA, GCS, APACHE II scores), and laboratory tests (white blood cell count, platelet count, red blood cell count, hemoglobin, red cell distribution width, glucose levels, creatinine, blood urea nitrogen, activated partial thromboplastin time, plasma prothrombin time, serum magnesium). Laboratory values were extracted as the first recorded measurement on the first day of ICU admission. We excluded variables with more than 30% missing values from the final cohort. Additionally, to reduce the issue of missing data, we employed multiple imputation using R packages for the variables.

### Statistical analysis

Continuous data that follow a normal distribution are presented as the mean ± standard deviation ($\bar{x}$ ± s), whereas categorical data are represented as percentages and analyzed using the $\chi^2$ test. Group comparisons for normally distributed data were made with the independent samples *t*-test. For non-normally distributed data, the median and interquartile range are reported, and comparisons between groups were performed using the Mann-Whitney *U* test. Categorical variables are expressed as numbers (%), and Fisher's exact test was used for analysis. PSM was employed to adjust the initially included data, using the nearest method with a caliper value of 0.05. Univariate Cox regression analysis was performed to include potential risk factors with $p < 0.05$ into a multivariate Cox regression analysis, generating a proportional hazards model with 28-day all-cause mortality as the primary outcome. Kaplan-Meier curves were generated to depict survival outcomes. Finally, subgroup analyses were performed based on age, race, gender, and comorbidities (hypertension, diabetes, acute kidney injury) following matched cohort analyses. For all analyses, a two-tailed $p < 0.05$ was considered statistically significant.

## Results

### Patient selection

Figure 1 illustrates the process of patient inclusion, exclusion, and grouping. A total of 24,673 patients were initially included. After excluding patients who did not meet the criteria, 3,539 patients were included in the cohort. Of these, 3,192

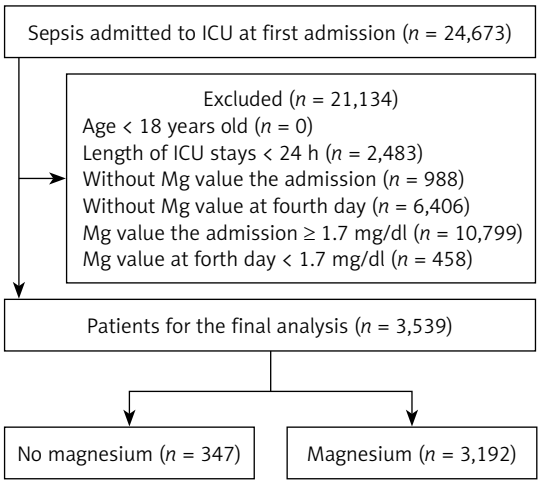


**Figure 1.** Chart of patient selection

**Table I.** Baseline characteristics before and after PSM

| Variable | Before PSM | | | | | After PSM | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total (*n* = 3539) | No magnesium (*n* = 347) | Magnesium (*n* = 3192) | *P*-value | SMD | Total (*n* = 650) | No magnesium (*n* = 325) | Magnesium (*n* = 325) | *P*-value | SMD |
| Age [years] | 63.60 ±17.05 | 64.73 ±16.40 | 63.48 ±17.12 | 0.192 | –0.074 | 64.42 ±16.95 | 65.27 ±16.38 | 63.57 ±17.48 | 0.201 | –0.097 |
| $SpO_2$ (%) | 96.99 ±4.46 | 96.78 ±3.92 | 97.01 ±4.52 | 0.345 | 0.053 | 96.97 ±3.75 | 96.77 ±3.97 | 97.17 ±3.50 | 0.170 | 0.115 |
| Heart rate [beats/min] | 94.00 (79.00, 110.00) | 95.00 (80.00, 108.00) | 94.00 (79.00, 111.00) | 0.812 | –0.003 | 94.00 (79.25, 108.00) | 94.00 (80.00, 108.00) | 93.00 (79.00, 107.00) | 0.306 | –0.088 |
| MBP [mm Hg] | 81.00 (69.00, 94.00) | 79.00 (67.00, 92.00) | 81.00 (70.00, 95.00) | 0.043 | 0.111 | 79.00 (67.00, 91.00) | 79.00 (67.00, 92.00) | 78.00 (67.00, 90.00) | 0.409 | –0.077 |
| Respiratory rate [beats/min] | 20.00 (16.00, 24.00) | 19.00 (16.00, 23.00) | 20.00 (16.00, 24.00) | 0.388 | 0.045 | 19.00 (16.00, 23.00) | 19.00 (16.00, 23.00) | 19.00 (16.00, 23.00) | 0.953 | –0.036 |
| Temperature [°C] | 36.78 (36.39, 37.22) | 36.83 (36.39, 37.28) | 36.78 (36.39, 37.22) | 0.276 | –0.096 | 36.83 (36.39, 37.22) | 36.83 (36.39, 37.28) | 36.83 (36.39, 37.17) | 0.612 | –0.088 |
| Charlson Comorbidity Index | 5.00 (3.00, 7.00) | 6.00 (4.00, 8.00) | 5.00 (3.00, 7.00) | < 0.001 | –0.267 | 5.00 (3.00, 7.00) | 5.00 (4.00, 8.00) | 5.00 (3.00, 7.00) | 0.072 | –0.099 |
| APSIII | 49.00 (37.00, 63.00) | 52.00 (40.00, 67.00) | 49.00 (37.00, 63.00) | 0.008 | –0.111 | 51.00 (41.00, 66.00) | 51.00 (38.00, 67.00) | 51.00 (42.00, 65.00) | 0.532 | 0.031 |
| OASIS | 35.00 (29.00, 41.00) | 34.00 (28.00, 40.00) | 35.00 (29.00, 41.00) | 0.034 | 0.140 | 35.00 (28.00, 40.00) | 35.00 (28.00, 40.00) | 34.00 (29.00, 40.00) | 0.932 | 0.009 |
| SOFA | 1.00 (0.00, 4.00) | 2.00 (0.00, 4.00) | 1.00 (0.00, 4.00) | 0.013 | –0.147 | 2.00 (0.00, 4.00) | 1.00 (0.00, 4.00) | 2.00 (0.00, 4.00) | 0.794 | 0.024 |
| SAPSII | 39.00 (31.00, 49.00) | 41.00 (33.00, 51.00) | 39.00 (31.00, 49.00) | 0.063 | –0.085 | 41.00 (33.00, 50.00) | 41.00 (33.00, 51.00) | 40.00 (32.00, 50.00) | 0.745 | –0.029 |
| GCS | 15.00 (15.00, 15.00) | 15.00 (15.00, 15.00) | 15.00 (15.00, 15.00) | < 0.001 | 0.146 | 15.00 (15.00, 15.00) | 15.00 (15.00, 15.00) | 15.00 (15.00, 15.00) | 0.683 | –0.016 |
| WBC [K/µl] | 11.50 (7.40, 16.30) | 10.90 (7.30, 15.80) | 11.60 (7.40, 16.40) | 0.402 | –0.029 | 11.35 (7.30, 16.70) | 11.00 (7.60, 15.80) | 11.80 (7.10, 17.10) | 0.557 | –0.009 |
| RBC [K/µl] | 3.54 (3.03, 4.08) | 3.38 (2.91, 4.01) | 3.55 (3.04, 4.08) | 0.005 | 0.149 | 3.49 (2.99, 4.09) | 3.42 (2.95, 4.02) | 3.55 (3.01, 4.14) | 0.129 | 0.112 |
| RDW (%) | 14.60 (13.60, 16.10) | 14.90 (13.90, 16.80) | 14.60 (13.60, 16.10) | < 0.001 | –0.212 | 14.90 (13.80, 16.70) | 14.90 (13.80, 16.70) | 15.00 (13.80, 16.60) | 0.896 | –0.021 |
| Platelet [K/µl] | 183.00 (124.00, 254.00) | 186.00 (123.50, 252.50) | 182.00 (124.00, 254.00) | 0.642 | –0.011 | 187.00 (124.00, 255.00) | 189.00 (126.00, 256.00) | 187.00 (120.00, 255.00) | 0.801 | 0.028 |

**Table I.** Cont.

| Variable | Before PSM | | | | | After PSM | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total (*n* = 3539) | No magnesium (*n* = 347) | Magnesium (*n* = 3192) | *P*-value | SMD | Total (*n* = 650) | No magnesium (*n* = 325) | Magnesium (*n* = 325) | *P*-value | SMD |
| BUN [mg/dl] | 18.00 (12.00, 28.00) | 23.00 (14.00, 35.00) | 18.00 (12.00, 27.00) | < 0.001 | –0.373 | 22.00 (14.00, 34.00) | 21.00 (14.00, 33.00) | 22.00 (14.00, 34.00) | 0.813 | 0.005 |
| Creatinine [mg/dl] | 1.00 (0.70, 1.50) | 1.10 (0.80, 2.00) | 1.00 (0.70, 1.50) | < 0.001 | –0.626 | 1.10 (0.80, 1.90) | 1.10 (0.80, 1.70) | 1.20 (0.80, 2.00) | 0.283 | 0.059 |
| PT [s] | 14.50 (12.90, 17.40) | 14.50 (13.00, 17.50) | 14.50 (12.80, 17.40) | 0.585 | –0.096 | 14.40 (13.00, 17.60) | 14.50 (12.90, 17.40) | 14.40 (13.10, 17.70) | 0.681 | –0.015 |
| APTT [s] | 31.40 (27.30, 38.70) | 31.60 (27.10, 41.00) | 31.40 (27.30, 38.50) | 0.640 | –0.011 | 31.90 (27.22, 38.90) | 31.00 (27.00, 40.30) | 32.30 (27.50, 38.40) | 0.549 | –0.083 |
| Mg | 1.50 (1.40, 1.60) | 1.60 (1.50, 1.60) | 1.50 (1.40, 1.60) | < 0.001 | –0.379 | 1.50 (1.40, 1.60) | 1.60 (1.50, 1.60) | 1.50 (1.40, 1.60) | < 0.001 | –0.091 |
| Gender, *n* (%) | | | | 0.856 | | | | | 0.637 | |
| Female | 1689 (47.73) | 164 (47.26) | 1525 (47.78) | | 0.010 | 304 (46.77) | 155 (47.69) | 149 (45.85) | | –0.037 |
| Male | 1850 (52.27) | 183 (52.74) | 1667 (52.22) | | –0.010 | 346 (53.23) | 170 (52.31) | 176 (54.15) | | 0.037 |
| Race, *n* (%) | | | | 0.077 | | | | | 0.865 | |
| Other | 1254 (35.43) | 108 (31.12) | 1146 (35.90) | | 0.100 | 198 (30.46) | 98 (30.15) | 100 (30.77) | | 0.013 |
| White | 2285 (64.57) | 239 (68.88) | 2046 (64.10) | | –0.100 | 452 (69.54) | 227 (69.85) | 225 (69.23) | | –0.013 |
| Congestive heart failure, *n* (%) | | | | 0.939 | | | | | 0.578 | |
| No | 2707 (76.49) | 266 (76.66) | 2441 (76.47) | | –0.004 | 498 (76.62) | 246 (75.69) | 252 (77.54) | | 0.044 |
| Yes | 832 (23.51) | 81 (23.34) | 751 (23.53) | | 0.004 | 152 (23.38) | 79 (24.31) | 73 (22.46) | | –0.044 |
| Hypertension, *n* (%) | | | | < 0.001 | | | | | 0.752 | |
| No | 2230 (63.01) | 188 (54.18) | 2042 (63.97) | | 0.204 | 358 (55.08) | 177 (54.46) | 181 (55.69) | | 0.025 |
| Yes | 1309 (36.99) | 159 (45.82) | 1150 (36.03) | | –0.204 | 292 (44.92) | 148 (45.54) | 144 (44.31) | | –0.025 |
| Diabetes, *n* (%) | | | | 0.004 | | | | | 0.249 | |
| No | 2471 (69.82) | 219 (63.11) | 2252 (70.55) | | 0.163 | 424 (65.23) | 205 (63.08) | 219 (67.38) | | 0.092 |
| Yes | 1068 (30.18) | 128 (36.89) | 940 (29.45) | | –0.163 | 226 (34.77) | 120 (36.92) | 106 (32.62) | | –0.092 |
| Malignant cancer, *n* (%) | | | | 0.154 | | | | | 1.000 | |
| No | 2961 (83.67) | 281 (80.98) | 2680 (83.96) | | 0.081 | 526 (80.92) | 263 (80.92) | 263 (80.92) | | 0.000 |
| Yes | 578 (16.33) | 66 (19.02) | 512 (16.04) | | –0.081 | 124 (19.08) | 62 (19.08) | 62 (19.08) | | 0.000 |

**Table I.** Cont.

| Variable | Before PSM | | | | | After PSM | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total (*n* = 3539) | No magnesium (*n* = 347) | Magnesium (*n* = 3192) | *P*-value | SMD | Total (*n* = 650) | No magnesium (*n* = 325) | Magnesium (*n* = 325) | *P*-value | SMD |
| AKI, *n* (%) | | | | 0.640 | | | | | 0.585 | |
| No | 582 (16.45) | 54 (15.56) | 528 (16.54) | | 0.026 | 99 (15.23) | 52 (16.00) | 47 (14.46) | | –0.044 |
| Yes | 2957 (83.55) | 293 (84.44) | 2664 (83.46) | | –0.026 | 551 (84.77) | 273 (84.00) | 278 (85.54) | | 0.044 |
| Vasoactive drug, *n* (%) | | | | < 0.001 | | | | | 0.530 | |
| No | 1514 (42.78) | 184 (53.03) | 1330 (41.67) | | –0.230 | 326 (50.15) | 167 (51.38) | 159 (48.92) | | –0.049 |
| Yes | 2025 (57.22) | 163 (46.97) | 1862 (58.33) | | 0.230 | 324 (49.85) | 158 (48.62) | 166 (51.08) | | 0.049 |
| Ventilator, *n* (%) | | | | < 0.001 | | | | | 0.829 | |
| No | 345 (9.75) | 62 (17.87) | 283 (8.87) | | –0.317 | 102 (15.69) | 50 (15.38) | 52 (16.00) | | 0.017 |
| Yes | 3194 (90.25) | 285 (82.13) | 2909 (91.13) | | 0.317 | 548 (84.31) | 275 (84.62) | 273 (84.00) | | –0.017 |
| CRRT, *n* (%) | | | | 0.029 | | | | | 0.891 | |
| No | 3284 (92.79) | 312 (89.91) | 2972 (93.11) | | 0.126 | 591 (90.92) | 295 (90.77) | 296 (91.08) | | 0.011 |
| Yes | 255 (7.21) | 35 (10.09) | 220 (6.89) | | –0.126 | 59 (9.08) | 30 (9.23) | 29 (8.92) | | –0.011 |

*$SpO_2$ – blood oxygen saturation, MBP – mean blood pressure, APSIII – Acute Physiology Score III, OASIS – Organization to Assess Strategies for Ischemic Syndromes, SOFA – Sepsis-Related Organ Failure Assessment Score, SAPSII – Simplified Acute Physiology Score II, GCS – Glasgow Coma Scale, WBC – white blood cells, RBC – red blood cells, RDW – red blood cell distribution width, BUN – blood urea nitrogen, PT – prothrombin time, APTT – activated partial thromboplastin time, AKI – acute kidney injury intra-aortic balloon pulsation, CRRT – continuous renal replacement therapy, Magnesium – use of magnesium.*

patients received magnesium sulfate infusion on the first day of ICU admission, and their magnesium levels were maintained at normal levels on the fourth day post-infusion, while 347 patients comprised the non-magnesium group.

### Baseline characteristics

Table I displays baseline characteristics before and after propensity score matching. In the overall cohort, patients who received magnesium sulfate infusion had higher average blood pressure, lower Charlson Comorbidity Index, APS III, and SOFA scores, higher OASIS scores, higher red blood cell counts, lower red blood cell distribution width, lower creatinine and blood urea nitrogen levels, fewer comorbidities of hypertension and diabetes, higher use of vasopressors and mechanical ventilation, and lower need for CRRT. Matching balanced the previously differing variables, and except for a statistically significant difference in magnesium ion levels ($p < 0.005$), all variables showed no differences after matching, ensuring baseline comparability and supporting the comparability of magnesium levels between the two groups.

### Main results

Table II shows the relationship between magnesium infusion and outcome variables (before and after PSM). The results indicate that after PSM, the magnesium sulfate treatment group had a significantly lower 28-day mortality rate than the untreated group (10.15% (33/3192) vs. 16.31% (53/347)), with a statistically significant difference ($p < 0.005$). Table III displays baseline characteristics for the 28-day survival and mortality groups. The results show that age (63.49 ±17.13 vs. 70.51 ±14.35 years), temperature (36.89 (36.39, 37.28) vs. 36.67 (36.25, 37.00)°C), Charlson Comorbidity Index (5.00 (3.00, 7.00) vs. 7.00 (5.00, 8.00)), APSIII (50.00 (39.00, 64.00) vs. 62.50 (51.00, 76.25)), OASIS (34.00 (28.00, 40.00) vs. 38.00 (30.25, 44.75)), SAPSII (40.00 (31.00, 49.00) vs. 49.00 (40.00, 56.75)), RBC (3.51 (3.02, 4.11) vs. 3.29 (2.88, 3.82) K/µl), RDW (14.80% (13.70, 16.40) vs. 15.90% (14.40, 17.70)), PT (14.30 (12.90, 17.22) vs. 15.80 (13.83, 20.30) s), and APTT (31.15 (27.10, 38.23) vs. 34.90 (28.47, 48.75) s) were lower in the 28-day survival group compared to the 28-day mortality group, all showing statistically significant differences ($p < 0.005$).

**Table II.** Association between magnesium and clinical outcomes

| Variables | Total | No magnesium | Magnesium | *P*-value |
|---|---|---|---|---|
| Before PSM | (*n* = 3539) | (*n* = 347) | (*n* = 3192) | |
| Primary outcome | | | | |
| 28-day mortality, *n* (%) | 483 (13.65) | 54 (15.56) | 429 (13.44) | 0.274 |
| Secondary outcomes | | | | |
| CRRT, *n* (%) | 255 (7.21) | 35 (10.09) | 220 (6.89) | 0.029 |
| Ventilator time [days] | 2.74 (1.02, 6.33) | 2.04 (0.45, 5.78) | 2.83 (1.08, 6.45) | < 0.001 |
| Hospital stay [days] | 12.69 (8.04, 20.89) | 12.29 (7.86, 21.11) | 12.70 (8.09, 20.87) | 0.714 |
| ICU stay [days] | 4.99 (2.69, 9.80) | 4.57 (2.52, 8.86) | 5.03 (2.71, 9.92) | 0.118 |
| Hospital mortality, *n* (%) | 439 (12.40) | 44 (12.68) | 395 (12.37) | 0.870 |
| ICU mortality, *n* (%) | 269 (7.60) | 23 (6.63) | 246 (7.71) | 0.472 |
| 90-day mortality, *n* (%) | 760 (21.47) | 88 (25.36) | 672 (21.05) | 0.063 |
| 365-day mortality, *n* (%) | 1095 (30.94) | 120 (34.58) | 975 (30.55) | 0.122 |
| After PSM | (*n* = 650) | (*n* = 325) | (*n* = 325) | |
| Primary outcome, *n* (%) | | | | |
| 28-day mortality | 86 (13.23) | 53 (16.31) | 33 (10.15) | 0.021 |
| Secondary outcomes | | | | |
| CRRT, *n* (%) | 59 (9.08) | 30 (9.23) | 29 (8.92) | 0.891 |
| Ventilator time [days] | 2.33 (0.61, 5.85) | 2.27 (0.54, 5.86) | 2.46 (0.79, 5.71) | 0.875 |
| Hospital stay [days] | 12.77 (7.99, 20.55) | 12.61 (7.89, 21.32) | 12.83 (8.16, 19.97) | 0.919 |
| ICU stay [days] | 4.59 (2.48, 8.76) | 4.73 (2.64, 8.99) | 4.46 (2.25, 8.37) | 0.115 |
| Hospital mortality, *n* (%) | 73 (11.23) | 43 (13.23) | 30 (9.23) | 0.106 |
| ICU mortality, n (%) | 35 (5.38) | 22 (6.77) | 13 (4.00) | 0.118 |
| 90-day mortality, *n* (%) | 146 (22.46) | 84 (25.85) | 62 (19.08) | 0.039 |
| 365-day mortality, *n* (%) | 205 (31.54) | 112 (34.46) | 93 (28.62) | 0.109 |

**Table III.** Baseline characteristics of the 28-day survival and 28-day mortality groups

| Variables | Total ($n$ = 650) | 28-day survival ($n$ = 564) | 28-day mortality ($n$ = 86) | $P$-value |
|---|---|---|---|---|
| Age [years] | 64.42 ±16.95 | 63.49 ±17.13 | 70.51 ±14.35 | < 0.001 |
| $SpO_2$ (%) | 96.97 ±3.75 | 96.92 ±3.75 | 97.33 ±3.73 | 0.346 |
| Heart rate [beats/min] | 94.00 (79.25, 108.00) | 94.00 (79.75, 108.00) | 93.00 (79.25, 106.00) | 0.719 |
| MBP [mm Hg] | 79.00 (67.00, 91.00) | 79.00 (67.00, 91.00) | 77.50 (66.00, 89.00) | 0.348 |
| Respiratory rate [beats/min] | 19.00 (16.00, 23.00) | 19.75 (16.00, 23.00) | 19.00 (16.00, 23.75) | 0.803 |
| Temperature [°C] | 36.83 (36.39, 37.22) | 36.89 (36.39, 37.28) | 36.67 (36.25, 37.00) | 0.006 |
| Charlson Comorbidity Index | 5.00 (3.00, 7.00) | 5.00 (3.00, 7.00) | 7.00 (5.00, 8.00) | < 0.001 |
| APSIII | 51.00 (41.00, 66.00) | 50.00 (39.00, 64.00) | 62.50 (51.00, 76.25) | < 0.001 |
| OASIS | 35.00 (28.00, 40.00) | 34.00 (28.00, 40.00) | 38.00 (30.25, 44.75) | < 0.001 |
| SOFA | 2.00 (0.00, 4.00) | 2.00 (0.00, 4.00) | 1.00 (0.00, 4.00) | 0.838 |
| SAPSII | 41.00 (33.00, 50.00) | 40.00 (31.00, 49.00) | 49.00 (40.00, 56.75) | < 0.001 |
| GCS | 15.00 (15.00, 15.00) | 15.00 (15.00, 15.00) | 15.00 (15.00, 15.00) | 0.860 |
| WBC [K/µl] | 11.35 (7.30, 16.70) | 11.30 (7.20, 16.27) | 12.36 (7.80, 18.00) | 0.158 |
| RBC [K/µl] | 3.49 (2.99, 4.09) | 3.51 (3.02, 4.11) | 3.29 (2.88, 3.82) | 0.042 |
| RDW (%) | 14.90 (13.80, 16.70) | 14.80 (13.70, 16.40) | 15.90 (14.40, 17.70) | < 0.001 |
| Platelet [K/µl] | 187.00 (124.00, 255.00) | 185.00 (122.00, 253.00) | 195.50 (154.00, 267.25) | 0.205 |
| BUN [mg/dl] | 22.00 (14.00, 34.00) | 22.00 (14.00, 33.00) | 23.50 (13.25, 37.75) | 0.418 |
| Creatinine [mg/dl] | 1.10 (0.80, 1.90) | 1.10 (0.80, 1.90) | 1.05 (0.80, 1.87) | 0.475 |
| PT [s] | 14.40 (13.00, 17.60) | 14.30 (12.90, 17.22) | 15.80 (13.83, 20.30) | < 0.001 |
| PTT [s] | 31.90 (27.22, 38.90) | 31.15 (27.10, 38.23) | 34.90 (28.47, 48.75) | 0.001 |
| Mg [mEq/l] | 1.50 (1.40, 1.60) | 1.50 (1.40, 1.60) | 1.50 (1.40, 1.60) | 0.519 |
| Dosage of magnesium [mg] | 100.00 (0.00, 200.00) | 200.00 (0.00, 200.00) | 0.00 (0.00, 200.00) | 0.051 |
| Gender, $n$ (%) | | | | 0.180 |
| No | 304 (46.77) | 258 (45.74) | 46 (53.49) | |
| Yes | 346 (53.23) | 306 (54.26) | 40 (46.51) | |
| Race, $n$ (%) | | | | 0.119 |
| No | 198 (30.46) | 178 (31.56) | 20 (23.26) | |
| Yes | 452 (69.54) | 386 (68.44) | 66 (76.74) | |
| Congestive heart failure, $n$ (%) | | | | 0.429 |
| No | 498 (76.62) | 435 (77.13) | 63 (73.26) | |
| Yes | 152 (23.38) | 129 (22.87) | 23 (26.74) | |
| Hypertension, $n$ (%) | | | | 0.751 |
| No | 358 (55.08) | 312 (55.32) | 46 (53.49) | |
| Yes | 292 (44.92) | 252 (44.68) | 40 (46.51) | |
| Diabetes, $n$ (%) | | | | 0.789 |
| No | 424 (65.23) | 369 (65.43) | 55 (63.95) | |
| Yes | 226 (34.77) | 195 (34.57) | 31 (36.05) | |
| Malignant cancer, $n$ (%) | | | | 0.005 |
| No | 526 (80.92) | 466 (82.62) | 60 (69.77) | |
| Yes | 124 (19.08) | 98 (17.38) | 26 (30.23) | |
| AKI, $n$ (%) | | | | 0.049 |
| No | 99 (15.23) | 92 (16.31) | 7 (8.14) | |
| Yes | 551 (84.77) | 472 (83.69) | 79 (91.86) | |
| Vasoactive, $n$ (%) | | | | < 0.001 |
| No | 326 (50.15) | 298 (52.84) | 28 (32.56) | |
| Yes | 324 (49.85) | 266 (47.16) | 58 (67.44) | |

**Table III.** Cont.

| Variables | Total (*n* = 650) | 28-day survival (*n* = 564) | 28-day mortality (*n* = 86) | *P*-value |
|---|---|---|---|---|
| Ventilator, *n* (%) | | | | 0.427 |
| No | 102 (15.69) | 91 (16.13) | 11 (12.79) | |
| Yes | 548 (84.31) | 473 (83.87) | 75 (87.21) | |
| CRRT, *n* (%) | | | | 0.013 |
| No | 591 (90.92) | 519 (92.02) | 72 (83.72) | |
| Yes | 59 (9.08) | 45 (7.98) | 14 (16.28) | |
| Magnesium, *n* (%) | | | | 0.021 |
| No | 325 (50.00) | 272 (48.23) | 53 (61.63) | |
| Yes | 325 (50.00) | 292 (51.77) | 33 (38.37) | |

*$SpO_2$ – blood oxygen saturation, MBP – mean blood pressure, APSIII – Acute Physiology Score III, OASIS – Organization to Assess Strategies for Ischemic Syndromes, SOFA – Sepsis-Related Organ Failure Assessment Score, SAPSII – Simplified Acute Physiology Score II, GCS – Glasgow Coma Scale, WBC – white blood cells, RBC – red blood cells, RDW – red blood cell distribution width, BUN – blood urea nitrogen, PT – prothrombin time, APTT – activated partial thromboplastin time, AKI – acute kidney injury intra-aortic balloon pulsation, CRRT – continuous renal replacement therapy, Magnesium – use of magnesium.*

**Table IV.** Univariate and multivariate Cox proportional analysis for 28-day mortality

| Variables | Univariate Cox regression | | Multivariate Cox regression | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Age [years] | 1.03 (1.01–1.04) | < 0.001 | | |
| Temperature [°C] | 0.74 (0.60–0.90) | 0.003 | | |
| Charlson Comorbidity Index | 1.17 (1.10–1.25) | < 0.001 | 1.17 (1.09–1.26) | < 0.001 |
| APSIII | 1.02 (1.01–1.03) | < 0.001 | 1.02 (1.01–1.03) | 0.001 |
| OASIS | 1.05 (1.03–1.08) | < 0.001 | | |
| SAPSII | 1.04 (1.02–1.05) | < 0.001 | | |
| RBC [K/µl] | 0.80 (0.61–1.05) | 0.102 | | |
| RDW [K/µl] | 1.14 (1.06–1.22) | < 0.001 | 1.08 (1.01–1.17) | 0.044 |
| PT [s] | 1.01 (0.99–1.03) | 0.202 | | |
| APTT [s] | 1.01 (1.01–1.02) | < 0.001 | 1.01 (1.01–1.02) | < 0.001 |
| Malignant cancer | | | | |
| No | 1.00 (Reference) | | | |
| Yes | 1.96 (1.24–3.11) | 0.004 | | |
| AKI | | | | |
| No | 1.00 (Reference) | | | |
| Yes | 2.12 (0.98–4.59) | 0.057 | | |
| Vasoactive drug | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 2.23 (1.42–3.51) | < 0.001 | 1.67 (1.03–2.71) | 0.037 |
| CRRT | | | | |
| No | 1.00 (Reference) | | | |
| Yes | 2.16 (1.22–3.82) | 0.009 | | |
| Magnesium | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 0.60 (0.39–0.93) | 0.021 | 0.61 (0.39–0.94) | 0.026 |

*APSIII – Acute Physiology Score III, OASIS – Organization to Assess Strategies for Ischemic Syndromes, SAPSII – Simplified Acute Physiology Score II, RBC – red blood cells, RDW – red blood cell distribution width, PT – prothrombin time, APTT – activated partial thromboplastin time, AKI – acute kidney injury intra-aortic balloon pulsation, CRRT – continuous renal replacement therapy, Magnesium – use of magnesium.*

Differences in the history of malignant cancer, AKI, vasoactive drugs, CRRT, and magnesium administration were also statistically significant between the two groups ($p < 0.005$). We then selected the significant factors for univariate and multivariate regression analyses. Table IV shows that the Charlson Comorbidity Index, APSIII, RDW, APTT, vasoactive drug use, and magnesium administration are independent risk factors for 28-day mortality in sepsis. Figure 2 shows the Kaplan-Meier survival curves for the exposure factors and 28-day mortality, both before and after PSM. The results indicate that the 28-day survival rate is higher in the magnesium sulfate treatment group compared to the untreated group.

## Secondary results

### 90-day mortality

Table II shows the relationship between magnesium infusion and outcome variables (before and after PSM). The results indicate that after PSM, the magnesium sulfate treatment group had a significantly lower 90-day mortality rate than the untreated group (19.08% (62/325) vs. 25.85% (84/325)), with a statistically significant difference ($p < 0.005$).

### Use of CRRT, mechanical ventilation time

No statistically significant differences were observed between magnesium sulfate infusion and the use of CRRT or mechanical ventilation time. The mortality rate with CRRT use was 19.08% in the magnesium infusion group and 25.85% in the non-magnesium group ($p = 0.891$). The mechanical ventilation time was 2.46 days for the magnesium group and 2.67 days for the control group ($p = 0.875$). Table II shows that, after PSM, no statistically significant differences were observed between the magnesium sulfate group and the non-treatment group in terms of the proportion using CRRT (29 (8.92%) vs. 30 (9.23%)) and mechanical ventilation time (2.46 (0.79, 5.71) vs. 2.27 (0.54, 5.86) days) ($p > 0.005$).

### Hospitalization time and ICU stay duration

Table II shows that, after PSM, no statistically significant differences were observed between the magnesium sulfate treatment group and the non-treatment group in terms of hospitalization time (12.83 (8.16, 19.97) vs. 12.61 (7.89, 21.32) days) and ICU stay duration (4.46 (2.25, 8.37) vs. 4.73 (2.64, 8.99) days) ($p > 0.005$).

### Hospital and ICU mortality rates

Table II shows that, after PSM, no statistically significant differences were observed between the magnesium sulfate treatment group and the non-treatment group in terms of hospital mortality rate (30 (9.23%) vs. 43 (13.23%)) and ICU mortality rate (13 (4.00%) vs. 22 (6.77%)) ($p > 0.005$).

### 365-day mortality rate

The 365-day mortality rate was 28.62% in the magnesium treatment group and 34.46% in the control group ($p = 0.109$). There were no statistically significant differences in 7-day mortality (3 (0.92%) vs. 8 (2.46%)), 14-day mortality (17 (5.23%) vs. 28 (8.62%)), and 365-day mortality (93 (28.62%) vs. 112 (34.46%)) between the magnesium treatment group and the untreated group after PSM ($p > 0.005$) (Table II).

### Subgroup analysis

Figure 3 presents the results of the subgroup analysis of 28-day all-cause mortality in the matched cohort. The subgroup analysis of the

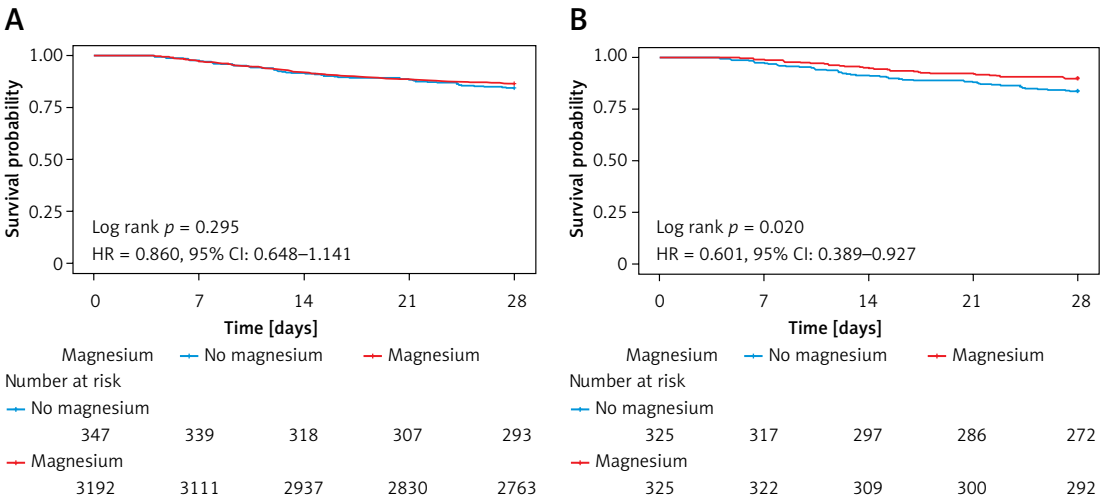


**Figure 2.** Kaplan-Meier curves matching 28-day mortality before and after PSM: **A** – before PSM, **B** – after PSM

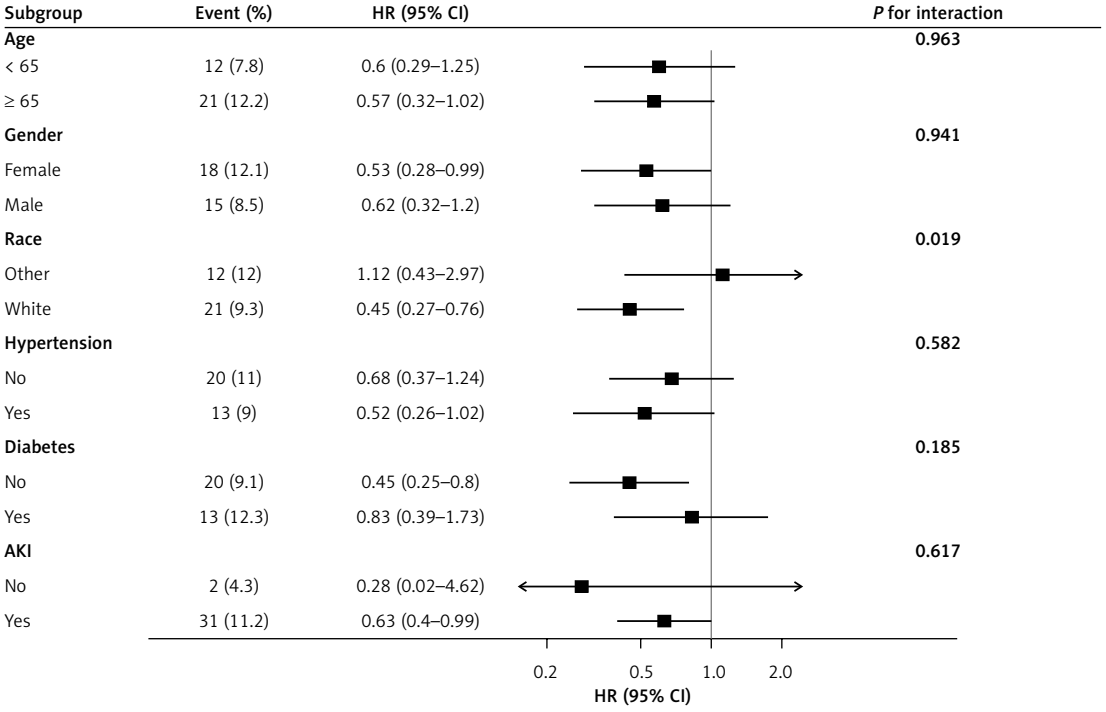


**Figure 3.** Subgroup analysis

matched cohort was based on age (< 65 vs. ≥ 65 years), sex (female vs. male), race (Caucasian vs. others), hypertension (yes vs. no), diabetes (yes vs. no), and acute kidney injury (yes vs. no). In both cohorts, the racial subgroup analysis showed that the 28-day all-cause mortality rate was lower in Caucasians (0.45% [0.27–0.76] vs. 1.12% [0.43–2.97]), and this difference was statistically significant ($p < 0.005$). No statistically significant differences were observed in the other subgroup analyses.

## Discussion

In this retrospective observational dataset, utilizing low-cost and readily available clinical variables, the current study results indicate that the use of magnesium sulfate can reduce the 28-day mortality and 90-day long-term mortality rates in patients with sepsis and concomitant hypomagnesemia. These findings suggest that the use of magnesium sulfate is a necessary and safe treatment option for patients with sepsis complicated by hypomagnesemia, significantly improving patient outcomes. Recently, Gu *et al.* reported in a retrospective study that the use of magnesium sulfate can reduce the 28-day mortality rate in patients with sepsis, which is consistent with our study findings [19]. The study by Gu *et al.* included patients with both hypomagnesemia and normal magnesium levels. Our research further separates these two subgroups, focusing specifically on the hypomagnesemic subgroup to better elucidate the role of magnesium supplementation strategies in critically ill patient populations with distinctly different characteristics. Previous studies have explored the relationship between magnesium supplementation in critically ill patients and the incidence and mortality of various diseases. In a randomized controlled trial, Noormandi *et al*. found that magnesium supplementation, which brought serum magnesium levels closer to normal, could shorten the time for lactate clearance in critically ill patients and reduce the 28-day mortality rate [20]. Khalili *et al.* similarly reported in a randomized controlled trial in 2021 that the incidence of AKI was lower in critically ill patients receiving magnesium sulfate infusion [17]. Barbosa *et al.* found in a randomized controlled trial that magnesium supplementation not only reduced the incidence of AKI in asymptomatic critically ill patients with hypomagnesemia but was also associated with a decrease in mortality [21]. Additionally, retrospective studies have confirmed that the use of magnesium sulfate can reduce mortality in patients with sepsis [18]. In conclusion, the administration of magnesium sulfate is associated with improved outcomes in critically ill patients.

Magnesium in the bloodstream is a key factor in the development of sepsis [22]. Ranking as the second most prevalent cation within cells, it is integral to a variety of vital physiological functions, such as controlling blood pressure, facilitating nerve signaling, enabling muscle contractions, maintaining cardiac excitability, and modulating immune responses [14, 23]. First, magnesium ions

may exert anti-inflammatory effects by inhibiting endotoxin-induced activation of NF-κB and the expression and release of substance P and other inflammatory molecules, acting as antagonists to calcium and effective L-type calcium channel blockers [24–26]. Second, studies have shown that magnesium ions can have a protective effect on multiple organs and reduce the incidence and mortality of sepsis and septic shock [27–29]. De Baaij *et al*. reported that magnesium ions can protect against the cardiac toxicity and liver and lung damage caused by lipopolysaccharides (LPS) [25]. At the cellular level in animal models, magnesium ions were found to inhibit pyroptosis, thereby protecting individuals from LPS-induced sepsis and septic shock [30]. In another animal study, it was found that magnesium ions could mitigate endothelial cell injury, coagulopathy, and lung injury mediated by circulating histones, thus reducing mortality in sepsis [31]. Third, magnesium ions play a crucial role as intracellular second messengers in the development and proliferation of T lymphocytes, thereby affecting the strength of individual immunity [24, 25]. Therefore, the use of magnesium sulfate is vital for the prognosis of patients.

However, the recognition and treatment of hypomagnesemia are not prioritized in current clinical practice. First, the use of magnesium supplements is quite limited. Previous data indicate that magnesium ion concentrations are below the normal range in many disease states, such as hypertension, diabetes, the incidence of gestational diabetes, arrhythmias, and congestive heart failure [11]. However, there are very few conditions for which magnesium supplements are considered first-line treatment, including torsades de pointes, acute exacerbations of asthma, and preeclampsia or eclampsia [8]. Second, there are no clear treatment guidelines for hypomagnesemia, leading clinicians to rely on experience for treatment. Although the incidence of hypomagnesemia is high in critically ill patients, especially in those with sepsis, there are currently no explicit treatment guidelines for hypomagnesemia; treatment options mainly depend on clinical symptoms and severity, with very limited use of magnesium sulfate [8, 19]. Third, hypomagnesemia is often overlooked. A survey by the European Society of Intensive Care Medicine indicated that 25.4% of surveyed intensive care specialists reported that they do not regularly monitor and/or administer intravenous magnesium in the early stages of critical illness, or measure magnesium levels no more than once a week [32]. Our findings can contribute relevant evidence to clinical theory and enhance clinicians' awareness of magnesium ion levels in critically ill patients, particularly those with sepsis, prompting closer monitoring of serum magnesium concentrations. When hypomagnesemia occurs in patients with sepsis, timely measures should be taken to actively supplement magnesium sulfate to improve patient outcomes.

There are several limitations of the current study that should be acknowledged. First, our study was retrospective, making it difficult to establish causal relationships between variables; thus, multicenter large-scale prospective studies are needed to further validate the conclusions. Second, the exact mechanism linking the correction of hypomagnesemia to improved outcomes in sepsis has not yet been elucidated. Third, this study only collected serum magnesium levels provided by the database; the analysis did not include factors such as intracellular magnesium levels, which might result in an incomplete representation of the body's total magnesium status.

In conclusion, we found that the Charlson Comorbidity Index, APS III, RDW, APTT, vasoactive drugs, and magnesium are independent risk factors for 28-day mortality in patients with sepsis. The use of magnesium sulfate can reduce the 28-day and 90-day mortality rates in patients with sepsis and concomitant hypomagnesemia, thereby improving long-term patient outcomes. This provides a theoretical basis for clinical practice and encourages clinicians to enhance management strategies for patients with sepsis and concomitant hypomagnesemia.

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## Declarations

The data utilized in this study were extracted from the MIMIC-IV (Medical Information Mart for Intensive Care IV) database, a publicly accessible and de-identified repository containing comprehensive clinical records from intensive care units (ICUs). MIMIC-IV encompasses information from over 70,000 ICU admissions at Beth Israel Deaconess Medical Center between 2001 and 2012. The dataset includes a wide range of variables, such as demographic details, laboratory measurements, medication administration, vital signs, diagnostic codes, treatment procedures, and nursing documentation. All data were handled in compliance with the MIMIC-IV usage guidelines, ensuring that ethical standards were met. The dataset is fully anonymized, with no identifiable patient information included. Prior to accessing the database, the necessary approvals were obtained, and all

research activities adhered strictly to the established access and usage protocols.

## Ethics approval

Not applicable.

## Conflict of interest

The authors declare no conflict of interest.

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