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Propensity score matched cohort study on magnesium supplementation and mortality in critically ill patients with HFpEF

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Heart failure with preserved ejection fraction (HFpEF) emerges as a singular subclass of heart failure, bereft of specific therapeutic options. Magnesium, an indispensable trace element, is essential to the preservation of cardiac integrity. However, the association between magnesium supplementation and mortality in HFpEF patients remains unclear. This study extracted HFpEF patient data from the MIMIC-IV database between 2008 and 2019. Propensity score matching was conducted to ensure that patients receiving magnesium supplementation (including magnesium sulfate and magnesium oxide) were balanced with those not receiving it in terms of baseline characteristics. The primary analysis focused on the 28-day all-cause mortality rate, with secondary endpoints encompassing ICU and one-year mortality rates, along with the duration of hospitalization. After matching, the study's final cohort balanced at 1970 patients, with 985 patients per group. The results showed that magnesium intake significantly contributed to a decrease in the 28-day all-cause mortality rate (hazard ratio [HR], 0.682; 95% confidence interval [CI], 0.539–0.863), particularly in subgroups such as older patients (HR, 0.65; 95% CI 0.52–0.81), females (HR, 0.55; 95% CI 0.41–0.73), and those with hypertension (HR, 0.62; 95% CI 0.48–0.79) or without diabetes (HR, 0.54; 95% CI 0.41–0.71). Although magnesium treatment improved both ICU and one-year mortality rates, it concurrently resulted in extended ICU and hospital stays. Mediation analysis indicated that blood urea nitrogen partially mediated the association between magnesium intake and mortality, accounting for approximately 22.73% of the observed effect. Magnesium supplementation has illustrated a significant potential for mitigating the mortality rate in the HFpEF patient, particularly among the elderly, female, and individuals with hypertension. Therefore, magnesium supplementation stands as a potentially valuable supplementary treatment modality for patients with HFpEF. Further comprehensive research is warranted to explore its effects more deeply.

Keywords Heart failure with preserved ejection fraction, Magnesium, Mortality, Propensity score matching, Blood urea nitrogen

Abbreviations

HFpEF	Heart failure with preserved ejection fraction
MIMIC-IV	Medical information mart in intensive care-IV
PSM	Propensity score matching
ICU	Intensive care unit
HR	Hazard ratio
CI	Confidence interval
ICD	International classification of diseases
LODS	Logistic organ dysfunction score
APSIII	Acute physiology score III

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SAPS-II	Simplified acute physiology score II
OASIS	Oxford acute severity of illness score
SOFA	Sequential organ failure assessment
SMD	Standardized mean difference
ACEI	Angiotensin-converting enzyme inhibitors
SD	Standard deviation
IQR	Interquartile range
OR	Odds ratios
MD	Median difference
BUN	Blood urea nitrogen

Heart failure with Preserved Ejection Fraction (HFpEF) emerges as a distinct subtype distinguished by its unique pathophysiological attributes, thereby demanding specialized therapeutic approaches distinct from other heart failure conditions[1–3]. Currently, pharmacological treatment for HFpEF primarily involves diuretics and blood pressure/blood glucose control, with no specific therapies targeting this condition[4]. Therefore, developing a simple, cost-effective medication for long-term treatment of HFpEF is extremely necessary.

As a vital mineral integral to human physiology, magnesium is paramount for sustaining the functionality of the cardiovascular, muscular, and nervous systems[5]. Nevertheless, the escalation in the consumption of deionized water and the cultivation of crops in soils deficient in magnesium has contributed to a significant reduction in dietary magnesium intake[6,7]. Investigations have demonstrated that approximately 50% of individuals in the United States, particularly the elderly, ingest magnesium quantities that fall short of the recommended dietary allowances, with nearly a quarter of US adults afflicted by hypomagnesemia[8,9]. Notably, HFpEF patients often have comorbidities such as diabetes and hypertension, which, combined with diuretic therapy, can accelerate magnesium metabolism, further exacerbating hypomagnesemia in these patients[10–13].

An increasing corpus of research posits a significant correlation between magnesium insufficiency and the pathogenesis as well as progression of heart failure[13–16]. However, the application of magnesium intake in the treatment of HFpEF remains controversial. Consequently, the objective of this study is to evaluate the impact of magnesium supplementation on mortality rates in patients with HFpEF and to explore its prospects as a treatment approach.

Methods

Study population

The MIMIC-IV database constitutes a comprehensive array of clinical datasets[17]. Prior to inclusion within the repository, exhaustive anonymization procedures are applied to all hospital admission records, guaranteeing the confidentiality and security of patient data. Access to this database is contingent upon successful completion of the National Institutes of Health's training program. The Institutional Review Board at Beth Israel Deaconess Medical Center has granted approval, reinforcing the research's ethical standards and exempting researchers from the requirement for further ethical review. Additionally, we confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Study population

In this study, we included patients diagnosed with HFpEF according to the International Classification of Diseases (ICD) 9th and 10th editions, who had at least one admission to the ICU. We specifically excluded patients with a diagnosis of acute myocardial infarction, hypertrophic cardiomyopathy, or those in stages 4 and 5 of chronic kidney disease (Supplementary Digital Content 1). Additionally, patients with ICU stays of less than 24 h and those with serum magnesium levels above 2.6 mg/dL prior to ICU admission were excluded. Furthermore, for patients with multiple ICU admissions, only the first record was analyzed.

Exposure and outcomes

The exposure of interest was the use of magnesium supplements, including magnesium oxide and magnesium sulfate. The primary outcome was 28-day all-cause mortality. Secondary outcomes included ICU mortality, 1-year mortality, ICU length of stay, and hospital length of stay.

Data extraction

For the extraction of patient data from the MIMIC-IV database, we employed structured SQL queries executed in the PostgreSQL environment, version 16.0. We collected demographic data, including age, sex, race, height, and weight. Clinical parameters included systolic and diastolic blood pressure, mean arterial pressure, heart rate, temperature, respiratory rate, blood oxygen saturation, and urine output. Laboratory parameters included white blood cell, hemoglobin, blood glucose, sodium, potassium, magnesium level, calcium, chloride, blood urea nitrogen (BUN), creatinine, red blood cell, and platelet. We calculated the severity scores for each patient, including the Logistic Organ Dysfunction Score (LODS), Acute Physiology Score III (APSIII), Simplified Acute Physiology Score II (SAPS-II), Oxford Acute Severity of Illness Score (OASIS), and Sequential Organ Failure Assessment (SOFA). We identified comorbidities, including chronic pulmonary disease, diabetes, renal disease, liver disease, malignant cancer, hypertension, sepsis, and atrial fibrillation. We also collected medication data, including angiotensin-converting enzyme inhibitors (ACEI: captopril, lisinopril, and ramipril), diuretics (furosemide, bumetanide, torsemide, hydrochlorothiazide, amiloride, and etacrynic acid), aldosterone receptor antagonists, and angiotensin receptor blockers (losartan potassium, olmesartan, and valsartan). A one-year longitudinal follow-up was conducted, with the collection of mortality statistics derived from integrated hospital and state record-keeping systems.

Propensity score matching

To mitigate the influence of possible confounding elements, we employed propensity score matching (PSM) to ensure comparable groups. The standardized mean difference (SMD) was utilized to measure the quality of matching, with a threshold of SMD < 0.10 demarcating satisfactory group balance. In the propensity score model, we incorporated a variety of factors such as age, weight, SAPS II, APSIII, OASIS, gender, race, SOFA, and LODS. We established three models to evaluate the effectiveness of magnesium intake: Model 1 was unadjusted; Model 2 adjusted for SAPS II, APSIII, LODS, SOFA, OASIS, BUN, age, race, and gender; and Model 3 further adjusted for additional variables, including blood oxygen saturation, ACEI use, renal disease, diabetes, sepsis, hypertension, malignant cancer, atrial fibrillation, urine output, heart rate, weight, systolic and diastolic blood pressure, respiratory rate, temperature, hemoglobin, white blood cell, red blood cell, creatinine, potassium, chloride, and calcium. Moreover, we ensured the robustness of our conclusions by carrying out comprehensive sensitivity analyses on the complete dataset, ensuring that our results were not influenced by potential biases.

Statistical analysis

Variables with a missing rate > 10% were deleted, and those with a missing rate < 10% were imputed using multiple imputation (Supplementary Digital Content 2). Variance inflation factors were used to detect multicollinearity between variables, and variables with high multicollinearity were removed, ensuring that all variables had a variance inflation factor < 5 (Supplementary Digital Content 3).

Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]) and analyzed with t-tests or Mann–Whitney U tests. Categorical variables were presented as counts and percentages and assessed with chi-squared or Fisher's tests. Kaplan–Meier analysis and log-rank tests assessed the 28-day all-cause mortality rates. Cox regression models calculated the hazard ratio (HR) and 95% confidence interval (CI) for the main outcome. Hodges-Lehmann estimates determined the median difference (MD) and 95% CI for continuous secondary outcomes. Mediation analysis, using the mediation package and bootstrap method, evaluated the CI for the mediation effect and the mediator's proportional contribution. We used R software (4.2.3, Vienna) for analyses, defining statistical significance as two-tailed P-values < 0.05.

Subgroup analyses

Subgroup and interaction analyses evaluated age (< 65 vs ≥ 65 years), gender, BUN (> 40 vs ≤ 40), systolic blood pressure (> 115 vs ≤ 115), diastolic blood pressure (> 60 vs ≤ 60), atrial fibrillation, diabetes, hypertension, renal disease (including chronic kidney disease, acute glomerulonephritis, hypertensive nephropathy, and renal tubulointerstitial disease), sepsis, SOFA score (> 4 vs ≤ 4), diuretic use, ACEI use, and ARB use on the primary outcome.

Results

Cohort characteristics

Figure 1 illustrates the patient selection process. After excluding ineligible records, the final cohort comprised 2605 patients, with 60.9% (1586) undergoing magnesium therapy. The matched cohort consisted of 1970 patients, with 985 per group. Among the entire cohort, magnesium therapy recipients were younger, exhibited reduced diabetes and renal disease incidence, showed higher APSIII scores, and were frequently treated with diuretics (Table 1). Matching improved variable balance, except for renal disease rates and diuretic use.

Magnesium regimen

In the entire cohort, the median duration of magnesium treatment was 3.3 h (IQR 1.6–6.6). A total of 30 patients received both magnesium sulfate and magnesium oxide, while 12 patients received only magnesium oxide, and 1544 patients received only magnesium sulfate. The median amount of magnesium supplementation in the treatment group was 1212 mg (approximately 6 g of magnesium sulfate), with a maximum value of 4040 mg. At baseline, the average magnesium level in the treatment group was 2.13 (SD 0.46) mg/dL, while in the non-treatment group, it was 2.09 (SD 0.28) mg/dL (P = 0.043). After magnesium administration, the magnesium level significantly increased (from 2.13 (SD 0.46) mg/dL to 2.46 (SD 0.84) mg/dL; P < 0.001). The daily dosage of magnesium sulfate was mostly 2 g or 4 g, and that of magnesium oxide was mostly 400 mg or 800 mg.

Main outcomes

The magnesium treatment group exhibited a 28-day mortality rate of 13.6% (134/985), which was markedly lower compared to the 20.3% (200/985) observed in the non-treatment group. Kaplan–Meier survival analysis revealed that magnesium supplementation significantly improved 28-day survival rates (P < 0.001, Fig. 2). In multivariate models, magnesium treatment was associated with lower 28-day mortality rates (Table 2): Model 1 (HR, 0.64; 95% CI 0.51–0.79; P < 0.001), Model 2 (HR, 0.68; 95% CI 0.54–0.85; P < 0.001), and Model 3 (HR, 0.68; 95% CI 0.54–0.86; P = 0.001).

Subgroup analysis

Figure 3 presents the subgroup analysis of 28-day mortality rates in the matched cohort. Notably, the effect of magnesium treatment varied across different subgroups. For patients under 65, magnesium therapy showed no significant impact on mortality (HR, 0.46; 95% CI 0.20–1.06; P = 0.067), whereas it significantly lowered the risk in the group over 65 (HR, 0.65; 95% CI 0.52–0.81; P < 0.001). Gender-specific analysis revealed that magnesium treatment significantly decreased mortality risk in female patients (HR, 0.55; 95% CI 0.41–0.73; P < 0.001), but not in male patients (HR, 0.78; 95% CI 0.56–1.10; P = 0.163). The presence of underlying diseases also influenced the effect of magnesium treatment. Regardless of whether patients had atrial fibrillation or sepsis, magnesium treatment was associated with a significant reduction in 28-day mortality risk. Magnesium treatment showed

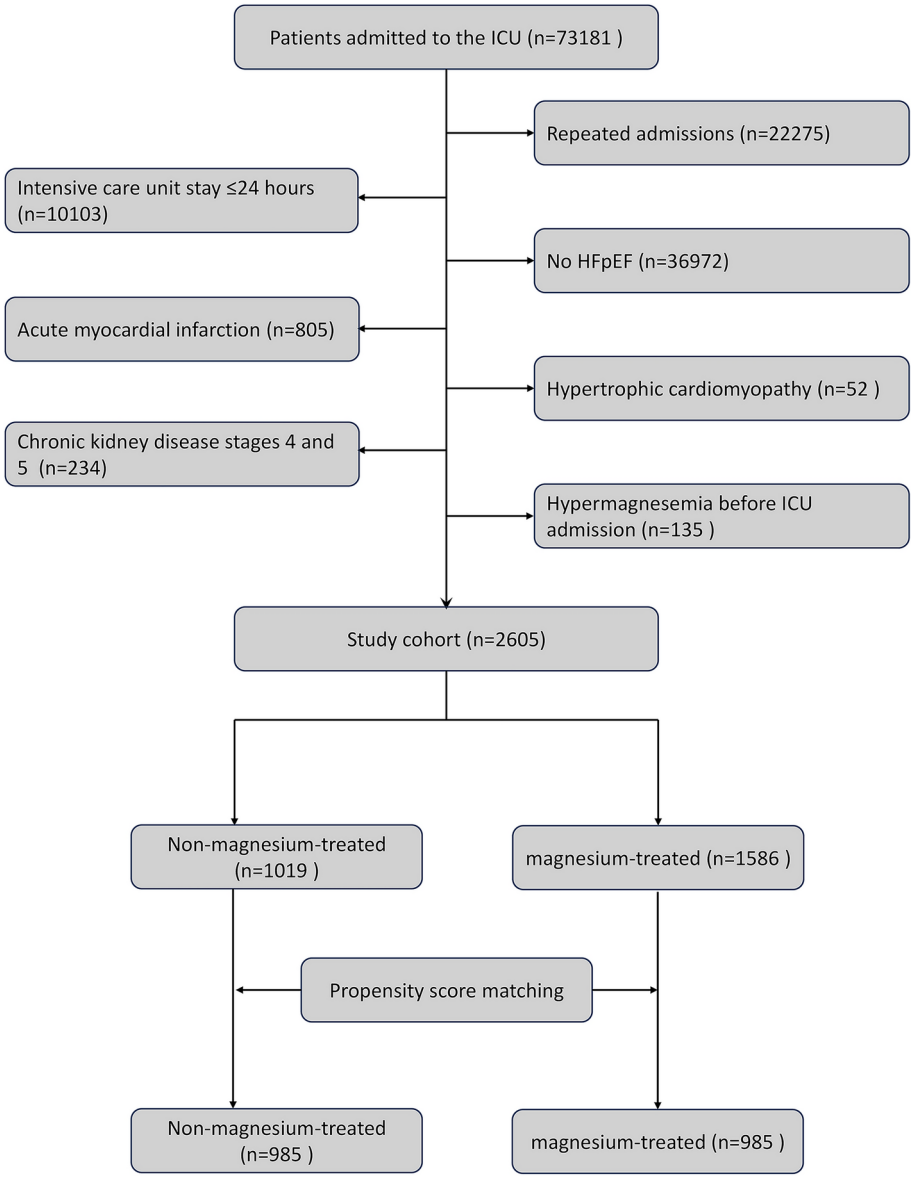

Fig. 1. Flow chart illustrating the process of patient selection in MIMIC-IV 2.2. *MIMIC-IV* the Medical Information Mart in Intensive Care-IV, *HFpEF* Heart failure with preserved ejection fraction, *ICU* intensive care unit.

a significant effect in patients with hypertension (HR, 0.62; 95% CI 0.48–0.79; P < 0.001) and in those without diabetes (HR, 0.54; 95% CI 0.41–0.71; P < 0.001).

Sensitivity analysis

In the sensitivity analysis, the 28-day mortality rate was 12.9% (205/1586) in the magnesium treatment group and 20.4% (208/1019) in the non-treatment group. The Kaplan–Meier curve showed that magnesium treatment reduced 28-day mortality (Supplementary Digital Content 4). Consistently, magnesium treatment was associated with lower 28-day mortality rates in all three models (Supplementary Digital Content 5): Model 1 (HR, 0.60; 95% CI 0.50–0.73; P < 0.001), Model 2 (HR, 0.71; 95% CI 0.57–0.87; P < 0.001), and Model 3 (HR, 0.71; 95% CI 0.57–0.87; P = 0.001). The subgroup analysis outcomes concurred with the PSM-matched cohort results, as presented in Supplementary Digital Content 6.

Secondary outcomes

The ICU mortality rate was significantly lower in the magnesium treatment group (5.8%, 57/985) compared to the non-treatment group (9.2%, 91/985). Multivariate analysis revealed that magnesium treatment was associated with reduced ICU mortality rates in all three models (Table 2): Model 1 (HR, 0.60; 95% CI 0.43–0.84; P = 0.003), Model 2 (HR, 0.64; 95% CI 0.45–0.90; P = 0.009), and Model 3 (HR, 0.62; 95% CI 0.44–0.89; P = 0.010). Similarly, the 1-year mortality rate was significantly lower in the magnesium treatment group (31.6%, 311/985) compared

Categories	Before propensity score matching			After propensity score matching		
	No-magnesium	Magnesium	SMD	No-magnesium	Magnesium	SMD
Number of patients	1019	1586		985	985	
Age (year)	76.73 (12.60)	74.99 (12.86)	0.137	76.56 (12.64)	76.79 (12.47)	0.019
Gender, n (%)			0.044			0.008
Female	573 (56.23)	857 (54.04)		553 (56.14)	557 (56.55)	
Male	446 (43.77)	729 (45.96)		432 (43.86)	428 (43.45)	
Race, n (%)			0.156			0.026
White	694 (68.11)	1158 (73.01)		684 (69.44)	693 (70.36)	
Black	120 (11.78)	118 (7.44)		102 (10.36)	95 (9.64)	
Asian	27 (2.65)	34 (2.14)		25 (2.54)	24 (2.44)	
Others	178 (17.47)	276 (17.40)		174 (17.66)	173 (17.56)	
Weight (lbs)	84.71 (30.30)	85.73 (28.81)	0.035	84.51 (30.04)	84.68 (28.83)	0.006
Severity of illness, n (%)						
SOFA	4 [2, 6]	4 [2, 7]	0.064	4 [2, 6]	4.00 [2, 6]	0.027
SAPS II	40.21 (12.22)	39.43 (11.94)	0.064	39.92 (11.98)	39.57 (12.07)	0.029
APS III	49.33 (17.52)	45.35 (17.37)	0.228	48.49 (16.73)	47.70 (17.47)	0.046
LODS	5 [3, 7]	5 [3, 6]	0.061	5 [3, 6]	4 [3, 7]	0.033
OASIS	32.84 (8.21)	32.79 (8.17)	0.006	32.73 (8.11)	32.88 (8.20)	0.018
Comorbidities, n (%)						
Atrial fibrillation	344 (33.76)	594 (37.45)	0.077	336 (34.11)	370 (37.56)	0.072
Chronic pulmonary disease	471 (46.22)	742 (46.78)	0.011	460 (46.70)	474 (48.12)	0.028
Diabetes	417 (40.92)	570 (35.94)	0.103	397 (40.30)	354 (35.94)	0.09
Hypertension	881 (86.46)	1332 (83.98)	0.07	850 (86.29)	846 (85.89)	0.012
Renal disease	402 (39.45)	440 (27.74)	0.25	387 (39.29)	286 (29.04)	0.217
Liver disease	86 (8.44)	126 (7.94)	0.018	84 (8.53)	70 (7.11)	0.053
Malignant cancer	125 (12.27)	165 (10.40)	0.059	123 (12.49)	101 (10.25)	0.07
Sepsis	590 (57.90)	926 (58.39)	0.01	567 (57.56)	568 (57.66)	0.002
Vital signs						
SBP (mmHg)	120.84 (18.24)	117.36 (15.23)	0.207	120.79 (18.21)	118.25 (15.91)	0.149
DBP (mmHg)	60.25 (11.07)	59.38 (10.54)	0.08	60.28 (11.07)	59.47 (10.86)	0.073
Heart rate (beats/min)	83.10 (16.32)	84.49 (15.82)	0.087	83.16 (16.29)	85.22 (16.79)	0.125
Respiratory rate (bpm)	20.22 (4.01)	19.88 (3.68)	0.089	20.22 (4.01)	20.03 (3.73)	0.048
SpO2 (%)	96.13 (2.18)	96.50 (2.09)	0.175	96.11 (2.17)	96.43 (2.14)	0.147
Temperature (℃)	36.74 (0.46)	36.80 (0.47)	0.133	36.75 (0.46)	36.79 (0.47)	0.097
Urine output (ml)	1619.05 (1097.74)	1825.18 (1274.85)	0.173	1621.42 (1102.90)	1827.61 (1291.32)	0.172
Laboratory tests						
Blood glucose (mg/dl)	142.63 (48.61)	141.45 (43.84)	0.025	142.04 (47.90)	142.82 (46.10)	0.017
White blood cell (10^9/L)	10.15 [7.50, 13.70]	11.50 [8.38, 15.35]	0.106	10.12 [7.40, 13.65]	11.10 [8.15, 14.90]	0.09
Platelet (10^9/L)	219.33 (96.39)	194.67 (90.46)	0.264	219.28 (96.11)	201.03 (91.93)	0.194
Hemoglobin (g/dl)	10.41 (1.97)	10.27 (1.84)	0.073	10.42 (1.96)	10.32 (1.84)	0.048
Red blood cell (10^{12}/L)	3.53 (0.69)	3.49 (0.66)	0.059	3.53 (0.68)	3.52 (0.66)	0.018
Creatinine (mg/dl)	1.25 [0.90, 2.00]	1.00 [0.80, 1.40]	0.41	1.23 [0.90, 1.97]	1.00 [0.80, 1.40]	0.394
BUN (mg/dl)	36.81 (24.77)	26.63 (16.99)	0.479	36.29 (23.95)	27.34 (17.34)	0.428
Potassium (mmol/l)	4.28 (0.58)	4.24 (0.55)	0.076	4.29 (0.59)	4.22 (0.55)	0.124
Calcium (mg/dl)	8.51 (0.69)	8.35 (0.64)	0.252	8.51 (0.69)	8.36 (0.64)	0.234
Sodium (mmol/l)	138.95 (5.27)	138.30 (4.64)	0.131	138.90 (5.09)	138.32 (4.78)	0.116
Chloride (mmol/l)	102.26 (6.67)	103.13 (6.19)	0.135	102.18 (6.52)	102.73 (6.34)	0.086
Magnesium level (mg/dl)	2.10 (0.30)	2.13 (0.47)	0.083	2.10 (0.30)	2.11 (0.46)	0.033
Continued						

Categories	Before propensity score matching			After propensity score matching		
	No-magnesium	Magnesium	SMD	No-magnesium	Magnesium	SMD
Drug therapy, n (%)						
Diuretic	489 (47.99)	889 (56.05)	0.162	473 (48.02)	544 (55.23)	0.145
Spironolactone	13 (1.28)	36 (2.27)	0.075	12 (1.22)	25 (2.54)	0.097
ACEI	97 (9.52)	140 (8.83)	0.024	92 (9.34)	95 (9.64)	0.01
ARB	41 (4.02)	73 (4.60)	0.029	39 (3.96)	48 (4.87)	0.044

Table 1. Comparison of baseline data before and after propensity score matching. *LODS* logistic organ dysfunction score, *APSIII* acute physiology score III, *SAPS-II* simplified acute physiology score II, *OASIS* oxford acute severity of illness score, *SOFA* sequential organ failure assessment, *SMD* standardized mean difference, BUN blood urea nitrogen, *SBP*, systolic blood pressure, *DBP*, diastolic blood pressure, *ACEI* angiotensin-converting enzyme inhibitor, *ARB*, angiotensin receptor blocker.

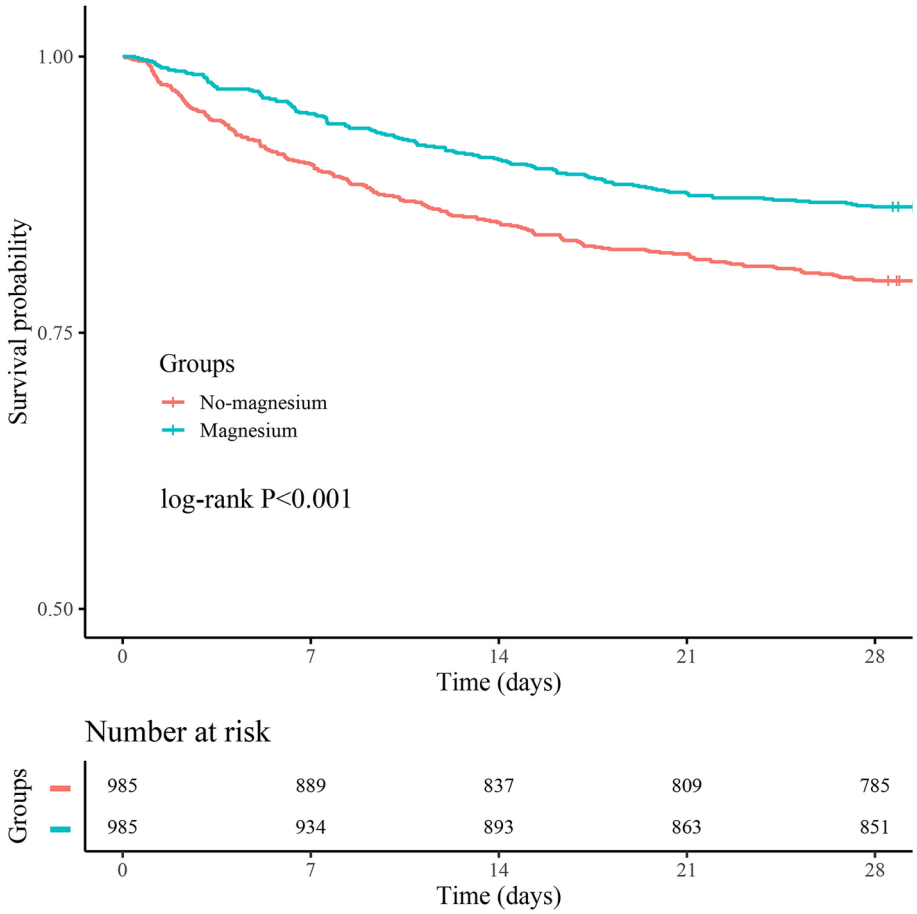

Fig. 2. Kaplan–Meier curves illustrate the 28-day all-cause mortality rates in the paired cohort based on magnesium intake.

to the non-treatment group (43.5%, 428/985). Multivariate analysis confirmed that magnesium treatment was associated with reduced 1-year mortality rates in all three models.

In the magnesium group, median stays were 2.9 days (IQR: 1.8–4.8) in the ICU and 8.9 days (IQR: 6.0–13.9) in the hospital, surpassing the non-treatment group's 2.6 days (IQR: 1.7–4.6) and 8.2 days (IQR: 5.1–12.9), respectively. Magnesium therapy corresponded with a statistically increase in both ICU (MD 0.16; 95% CI 0.02–0.29; P = 0.022) and hospital (MD 0.84; 95% CI 0.34–1.28; P < 0.001) lengths of stay.

Mediation analysis of BUN

The mediation analysis focused on BUN's influence on the relationship between magnesium intake and mortality in HFpEF patients, as shown in Fig. 4. The results showed that magnesium intake had a significant indirect effect on mortality through its influence on BUN levels, with an indirect effect size of − 0.014 (P < 0.001). Controlling

Categories	Model 1		Model 2		Model 3	
	HR/MD (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Primary outcome						
28-day mortality#	0.64 (0.51–0.79)	< 0.001	0.68 (0.54–0.86)	< 0.001	0.68 (0.54–0.86)	0.001
Secondary outcomes						
ICU mortality#	0.60 (0.43–0.84)	0.003	0.63 (0.45–0.90)	0.009	0.62 (0.44–0.89)	0.010
1-year mortality#	0.66 (0.57–0.77)	< 0.001	0.71 (0.61–0.83)	< 0.001	0.74 (0.63–0.87)	< 0.001
LOS in ICU*	0.16 (0.02–0.29)	0.022	–	–	–	–
LOS in hospital*	0.84 (0.34–1.28)	< 0.001	–	–	–	–

Table 2. Association of magnesium use in the matched cohort with primary and secondary outcomes. Model 1: unadjusted; Model 2: adjusted for SAPS II, APSIII, LODS, SOFA, OASIS, BUN, age, race, and gender; Model 3: further adjusted for additional variables, including urine output, heart rate, weight, systolic and diastolic blood pressure, respiratory rate, temperature, blood oxygen saturation, ACEI use, renal disease, diabetes, sepsis, hypertension, malignant cancer, atrial fibrillation, hemoglobin, white blood cell count, red blood cell count, creatinine, potassium, chloride, and calcium level. *CI* confidence interval, *HR* hazard ratio, *MD* median difference, *LOS* length of stay. #HR was calculated using Cox proportional hazards model. *MD was calculated using Hodges-Lehmann estimator.

for BUN, SOFA score, urine output, age, weight, RBC, respiratory rate, chloride, SpO2, race, and creatinine, magnesium intake significantly influenced mortality ($P < 0.001$), suggesting a direct effect. The mediation analysis revealed that BUN mediated approximately 22.7% (95% CI 11.7–50.0%; $P < 0.001$) of the effect of magnesium intake on mortality (Table 3).

Discussion

This retrospective propensity score-matched cohort study investigated the association between magnesium treatment and mortality in patients with HFpEF. Magnesium therapy was linked to a marked reduction in 28-day mortality, offering pronounced advantages for older adults, individuals with high blood pressure, and female patients. Furthermore, BUN was found to mediate the relationship between magnesium intake and mortality. Our findings suggest that magnesium treatment may be an effective intervention for HFpEF, but further randomized controlled trials are needed to validate its long-term efficacy and safety.

The primary finding of this study indicates that critically ill patients with HFpEF who received magnesium therapy experienced a significant reduction in the 28-day mortality. Currently, no articles have been identified that explore the association between magnesium intake and HFpEF. A search of the American Clinical Trials Registry revealed only one prospective cohort study (ClinicalTrials.gov ID NCT06353750) examining the impact of magnesium supplementation on myocardial and skeletal muscle metabolism and energetics at rest and under stress in HFpEF patients; this study is expected to be completed by 2026. Given that HFpEF accounts for approximately 50% of heart failure cases, we can also gain indirect insights from the association between magnesium intake and heart failure overall[18,19]. Two animal studies conducted by Liu's team demonstrated that mice with low magnesium levels exhibited impaired cardiac diastolic function, a significant reduction in ATP levels within cardiomyocytes, and mitochondrial dysfunction characterized by excessive production of mitochondrial reactive oxygen species and depolarization of the mitochondrial membrane potential[20]. Additionally, the myocardial myosin-binding protein C in the hearts of these low-magnesium mice underwent S-glutathionylation[21]. Notably, when these mice were supplemented with sufficient magnesium, all these abnormalities returned to normal[20,21]. A randomized controlled study further found that sodium-glucose cotransporter-2 inhibitors improved heart failure outcomes while also increasing serum magnesium levels during treatment, suggesting that serum magnesium levels may play a significant role in heart failure prognosis[22]. Furthermore, a study involving over 4,000 individuals indicated that magnesium levels are inversely associated with the risk of major cardiovascular diseases, heart failure, atrial fibrillation, and microvascular complications[23]. Moreover, a single-center observational study has shown that patients with lower serum magnesium levels are at a higher risk of heart failure, reinforcing the importance of magnesium in the cardiovascular outcomes of HFpEF patients[24]. Collectively, these findings indirectly suggest that magnesium intake may be beneficial in the context of HFpEF.

Although our secondary outcomes suggest that HFpEF patients receiving magnesium supplementation had slightly longer stays in the ICU and overall hospitalization compared to those not supplemented with magnesium, with the difference being statistically significant, the numerical gap between the groups is minimal. Consequently, we deem this difference to have negligible clinical significance.

Subgroup analysis revealed that magnesium supplementation had a more pronounced effect in reducing mortality risk in elderly patients and female patients, which may be attributed to the fact that the magnesium levels of these populations are more susceptible to influence[25–27]. Furthermore, subgroup analysis also uncovered the potential impact of underlying diseases on the therapeutic effect of magnesium supplementation, where patients with hypertension were more likely to benefit from magnesium intake, with a potential mechanism related to magnesium's blood pressure-lowering effect[28,29]. In contrast, magnesium intake did not demonstrate any benefits in the diabetic patient subgroup.

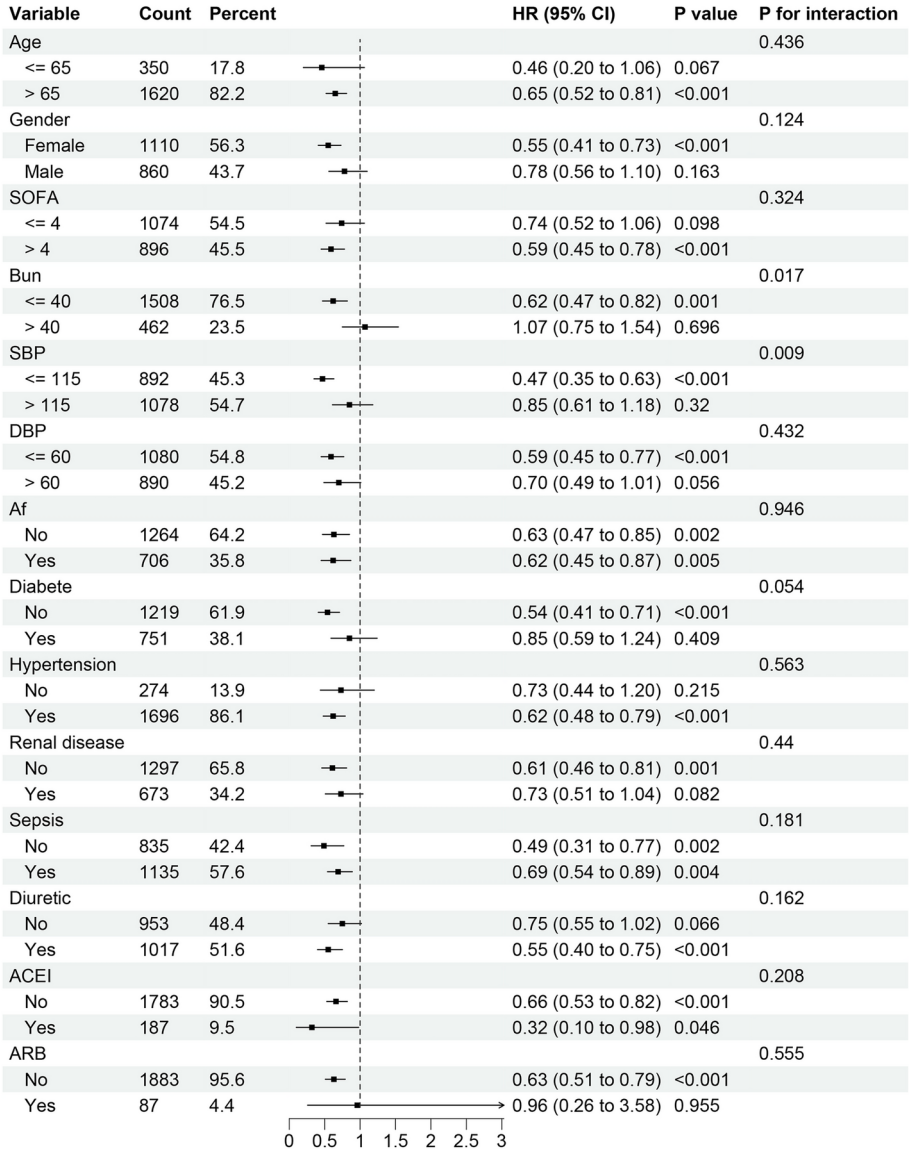

Fig. 3. Analysis of subgroups for 28-day all-cause mortality in the matched cohort. *CI* confidence interval, *HR* hazard ratio, *SOFA* sequential organ failure assessment, *BUN* blood urea nitrogen, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *Af* atrial fibrillation, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker.

The findings of this study indicate that magnesium supplementation is associated with reduced mortality rates in the overall population of patients with HFpEF. However, no significant benefits were observed in the specific subgroups of younger patients and male patients. This discrepancy may be attributed to the relatively robust renal function in younger patients, which subsequently influences the metabolism of magnesium; whereas in male patients, differences in hormone levels may represent another factor affecting the efficacy of magnesium.

Our study suggests that renal function (blood urea nitrogen) may play a role in the reduction of mortality risk associated with magnesium intake. Magnesium may exert a protective effect by inhibiting phosphate-induced renal injury, reducing cell apoptosis and inflammation, and thereby slowing down the progression of renal damage[30–32]. A retrospective observational cohort study has shown that low serum magnesium levels are associated with a higher incidence of acute kidney injury in patients undergoing cardiac surgery[33]. In addition to its mediating effect on renal function, magnesium intake may also reduce oxidative stress in the heart, lowering the risk of arrhythmia[20,34]. Inflammation is a key factor in the progression of heart failure, and magnesium may alleviate the severity of heart failure by decreasing the levels of inflammatory mediators[35,36].

The mediation analysis revealed that BUN partially mediated the relationship between magnesium supplementation and mortality in HFpEF patients, accounting for approximately 22.73% of the observed effect. This finding is significant because it suggests that the renal function, as reflected by BUN levels, plays a role in the mortality benefits observed with magnesium supplementation. Elevated BUN levels are indicative of impaired renal function, which is known to be associated with worse outcomes in heart failure patients. The mediating

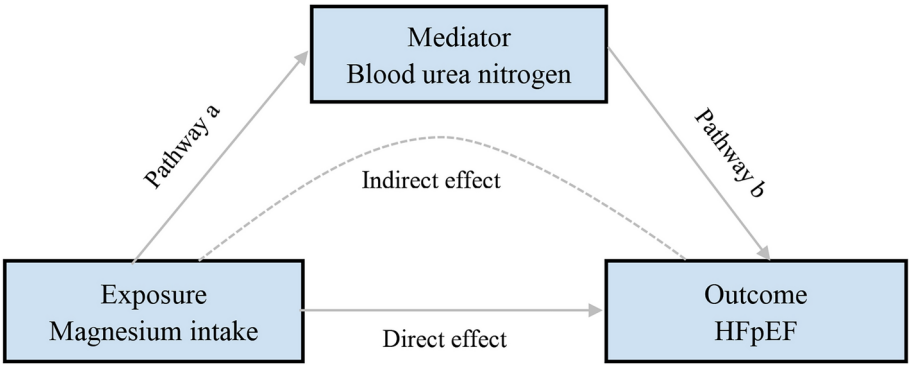

Fig. 4. Mediated analysis model path diagram. Notes: Magnesium intake is defined as the independent variable; HFpEF as the dependent variable; and BUN as the mediating variable. Path a represents the regression coefficient of the association between magnesium intake and BUN. Path b represents the regression coefficient of the association between BUN and HFpEF. The total effect of magnesium intake on HFpEF is the sum of the direct effect and the indirect effect.

Variable	Total effect	Indirect effect	Direct effect	Proportion mediated
β	− 0.060	− 0.014	− 0.046	22.7%
(95% CI)	− 0.090, − 0.030	− 0.020, − 0.010	− 0.077, − 0.020	11.7–50.0%
P-value	< 0.001	< 0.001	0.002	< 0.001

Table 3. Association between magnesium intake and HFpEF: the mediating role of blood urea nitrogen.

effect of BUN implies that the renal protective effects of magnesium may contribute to its mortality-reducing effects. This is clinically relevant because it highlights the potential for magnesium to exert beneficial effects on renal function, which could be a key mechanism underlying its impact on mortality in HFpEF patients. Future studies should further investigate the interplay between magnesium supplementation, renal function, and outcomes in HFpEF to better understand and leverage this relationship.

Clinical significance of magnesium supplementation

Magnesium supplementation, as a simple and inexpensive therapeutic approach, offers potential new treatment options for clinicians in the management of HFpEF. Given the lack of specific medications for HFpEF patients, magnesium supplementation may provide an effective intervention to improve their prognosis. However, further research is needed to determine the optimal dosage, treatment duration, and patient selection criteria for magnesium therapy.

Based on our study findings, it is recommended to consider magnesium supplementation in the clinical management of patients with HFpEF, particularly for those with comorbidities such as hypertension and elderly female patients. Given the observed reduction in 28-day mortality, it is suggested to initiate magnesium supplementation early in the course of ICU treatment, while closely monitoring for potential adverse reactions and renal function. However, the decision to supplement magnesium should be individualized, taking into account the patient's overall clinical condition, renal function, and the potential risks and benefits.

Limitations of the study

Despite using the PSM method to reduce bias, limitations persist in our study. First, as a retrospective cohort study, we cannot completely eliminate the potential impact of unmeasured confounding factors. Second, the database lacked detailed information on the indications and discontinuation of magnesium supplementation, which may have affected the accuracy of our assessment of its therapeutic effects. Furthermore, our study did not assess the long-term impact of magnesium supplementation on cardiac structure and function. Based on our findings, future studies should further explore the optimal dosage and treatment regimens of magnesium supplementation, as well as its therapeutic effects in different subtypes of HFpEF. Additionally, randomized controlled trials are needed to validate the long-term efficacy and safety of magnesium supplementation. It is important to note that, given the ICU setting of our study, the findings may not be generalizable to broader populations outside the ICU. Therefore, future research should extend to more diverse patient populations to confirm the effects of magnesium supplementation. Finally, with the emergence of new therapeutic options, such as the clinical trial results for drugs like Finerenone, a new perspective has been offered for the treatment of HFpEF[37]. These studies may introduce new dimensions to our understanding and should be considered in the design of future research to comprehensively evaluate the relative benefits and safety of various treatment strategies.

Conclusions

In conclusion, our propensity score-matched cohort study specifically demonstrates that magnesium supplementation is significantly associated with reduced 28-day mortality in critically ill patients with HFpEF. This association was particularly pronounced in subgroups such as older adults, females, and individuals with hypertension, suggesting that magnesium supplementation could be a valuable therapeutic strategy in these specific patient populations. However, it is important to note that our findings should not be generalized to all HFpEF patients without further investigation. Our study highlights the need for additional research to determine the optimal dosage, duration of treatment, and patient selection criteria for magnesium therapy. Future randomized controlled trials are essential to confirm the long-term efficacy and safety of magnesium supplementation in HFpEF management, and to establish its role in the broader clinical context.

Data availability

The MIMIC-IV2.2 database offers public access to the complete data set from this study.

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Author contributions
Study conception and design: LJS and JJY; data acquisition and analysis: LJS and ML; drafted the manuscript: LJS and ML; interpreted data and made critical revisions of the manuscript: LY and CLZ. All the authors have read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The use of the MIMIC-IV 2.2 database for this study was authorized by the ethical review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Considering the publicly accessible nature of the data contained within the MIMIC-IV 2.2 database, our study was granted exemption from obtaining additional ethical approval and informed consent requirements.

Additional information
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