

Original Article

Prior use of dihydropyridines is associated with reduced mortality among patients with sepsis in the intensive care unit: a retrospective cohort study using the MIMIC-IV database

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Abstract: Objectives: Evidence regarding the survival benefits of dihydropyridine calcium channel blockers in patients with sepsis is limited. This study aimed to investigate whether prior use of dihydropyridines is associated with improved survival in patients with sepsis in the intensive care unit (ICU). Methods: We extracted relevant information on patients diagnosed with sepsis from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (version 2.0). Patients were divided into a dihydropyridine group and a no-dihydropyridine group based on drug prescription records. The primary outcomes were 30-day, 60-day, and 90-day mortality. After propensity score matching, univariate and multivariable-adjusted Cox proportional hazards models were used to assess the association between dihydropyridine calcium channel blocker use and survival in patients with sepsis. Results: A total of 20,796 patients were included in the analysis. After propensity score matching, 1,232 patients who had used dihydropyridines and 1,232 who had not were included. Multivariable-adjusted Cox proportional hazards models showed that prior use of dihydropyridines was significantly associated with reduced 30-day (hazard ratio [HR], 0.800; 95% confidence interval [CI], 0.662-0.968; $P = 0.021$), 60-day (HR, 0.776; 95% CI, 0.653-0.922; $P = 0.004$), and 90-day (HR, 0.760; 95% CI, 0.645-0.895; $P = 0.001$) mortality. Conclusions: In this retrospective cohort study, prior use of dihydropyridines was associated with improved survival among patients with sepsis in the ICU.

Keywords: Dihydropyridines, calcium channel blockers, sepsis, mortality, MIMIC-IV database

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. It is a major public health concern characterized by increasing incidence and high mortality [2, 3]. The reported annual standardized incidence of sepsis increased from 328 to 422 per 100,000 people between 2017 and 2019 [4]. The high mortality associated with sepsis remains a major challenge for clinicians, with reported mortality rates of 26.7% in hospitalized patients and 41.9% among patients treated in the intensive care unit (ICU) [5]. Therefore, there is an urgent need to improve the management of sepsis and reduce

its substantial burden, particularly in the ICU [6].

Dihydropyridines (DHPs) are a class of calcium channel blockers (CCBs). CCBs can be broadly categorized into two main classes according to their primary sites of action: dihydropyridines and non-dihydropyridines. DHPs, including amlodipine, nifedipine, nicardipine, and nimodipine, are more widely used in clinical practice than non-dihydropyridines. DHPs relax vascular smooth muscle by reducing intracellular calcium concentrations, thereby lowering blood pressure; thus, they are commonly used to treat hypertension [7]. In addition, DHPs have a greater relative effect on vascular

Table 1. The details of dihydropyridines

Drugs	Percentage (%)
Amlodipine	84.02
Nifedipine	11.99
Nimodipine	2.38
Felodipine	1.08
Nicardipine	0.49
Isradipine	0.05

smooth muscle than on the heart and therefore exert less influence on cardiac autonomic activity, heart rate, and cardiac conduction [8]. DHPs may also have beneficial effects in the treatment of coronary heart disease [9, 10].

Previous studies have suggested that DHPs may influence outcomes in animal models of sepsis. Amlodipine exerts protective effects in rat models of endotoxemia and sepsis by inhibiting the production of pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) [11, 12]. Pretreatment with amlodipine can also prevent lipopolysaccharide-induced vascular hyporeactivity in rats [13]. Nifedipine has been reported to inhibit the inflammatory response in a rat model of septic shock by modulating malondialdehyde (MDA) and superoxide dismutase (SOD) levels [14].

However, knowledge regarding the association between DHP use and outcomes in patients with sepsis is limited. One study suggested that preadmission use of DHPs was associated with improved 30-day survival among patients with sepsis, but that study included a relatively small number of patients (387 CCB users) [15].

Here, we conducted an observational study of 20,796 patients using data from the large MIMIC-IV database. This study aimed to investigate the association between prior DHP use and outcomes among patients with sepsis in the ICU. In addition, we conducted subgroup analyses to explore whether this association differed across clinically characterized subgroups of patients with sepsis.

Materials and methods

Data source

Data for this retrospective cohort study were extracted from the Medical Information Mart

for Intensive Care IV (MIMIC-IV) database (version 2.0). MIMIC-IV is a large, publicly available database containing de-identified data from patients admitted to the intensive care units of Beth Israel Deaconess Medical Center (Boston, USA) between 2008 and 2019. The database contains comprehensive health-related information from 76,943 ICU admissions, including demographic characteristics, vital signs, laboratory measurements, medication administration, diagnoses, and treatments.

After completing the CITI Data or Specimens Only Research training course, we obtained permission to access the MIMIC-IV database (record ID: 50199917). The collection of patient information and creation of the research resource were reviewed by the Institutional Review Board of Beth Israel Deaconess Medical Center, which granted a waiver of informed consent and approved the data-sharing initiative.

Study population

Patients with an admission diagnosis of sepsis were included in this study. Sepsis was defined according to the Sepsis-3 criteria as suspected infection accompanied by a Sequential Organ Failure Assessment (SOFA) score ≥ 2 . The diagnosis time was restricted to the period from 24 hours before to 24 hours after ICU admission.

The exclusion criteria were as follows: age < 18 years; ICU length of stay < 24 hours; death within the first 24 hours of ICU stay; or missing covariate data. For patients with multiple ICU admissions for sepsis, only the first admission was included.

Drug exposure

Patients were divided into two groups in this study: the dihydropyridine group (DHP group), comprising patients who had used a dihydropyridine within 1 month before ICU admission, and the no-dihydropyridine group (no-DHP group), comprising patients who had not used a dihydropyridine during that period. The specific types of DHPs included in the study are provided in the Supplementary Material (Table 1).

Outcomes

The primary outcomes were 30-day, 60-day, and 90-day mortality. The secondary outcome was ICU length of stay.

Covariates

To balance baseline characteristics between groups and reduce potential confounding, the following covariates were included in propensity score matching and multivariable-adjusted Cox proportional hazards models. A total of 33 covariates recorded within the first 24 hours after ICU admission were extracted, including demographics (age, gender, race, and weight); vital signs (heart rate, mean arterial pressure, respiratory rate, peripheral oxygen saturation [SpO₂], and temperature); laboratory results (hemoglobin, platelet count, white blood cell count, blood urea nitrogen, serum creatinine, glucose, anion gap, and bicarbonate); disease severity scores (Glasgow Coma Scale [GCS] and SOFA score); and comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, renal disease, diabetes, rheumatic disease, peptic ulcer disease, dementia, paraplegia, cancer, and acquired immunodeficiency syndrome [AIDS]).

Statistical analysis

Categorical variables were presented as counts and percentages, whereas continuous variables were presented as means (standard deviations) or medians (interquartile ranges), as appropriate.

Propensity score matching was performed to account for potential confounding. Matching was conducted at a 1:1 ratio without replacement using a nearest-neighbor matching algorithm, with a caliper width of 0.2 (MatchIt package in R). The balance of covariate distributions between groups was assessed before and after matching using the Wilcoxon rank-sum test, Pearson's chi-square test, or Fisher's exact test, as appropriate. A *P* value >0.05 was considered indicative of acceptable balance.

In the matched cohort, 30-day, 60-day, and 90-day mortality were compared between groups using univariate and multivariable-adjusted Cox proportional hazards models. Covariates with *P*<0.05 in the univariate analysis were included in the multivariable-adjusted Cox proportional hazards models. ICU length of stay was analyzed using the Wilcoxon rank-sum test. Subgroup analyses were per-

formed to examine the association between DHP use and outcomes across different clinically characterized subgroups of patients with sepsis.

All statistical analyses were performed using R (version 4.2.3). Statistical significance was defined as a two-sided *P* < 0.05.

Results

Patients

A total of 32,050 ICU admissions with a diagnosis of sepsis were identified in the MIMIC-IV database. The detailed patient selection process is shown in **Figure 1**. Ultimately, 20,796 patients were included in the analysis, of whom 1,234 (5.93%) had used DHPs within 1 month before ICU admission. Amlodipine was the most commonly prescribed DHP (84.02%), followed by nifedipine (11.99%) (**Table 1**). Baseline characteristics of patients in the DHP and no-DHP groups are presented in **Table 2**.

Propensity score matching

Propensity score matching was performed to balance baseline characteristics between the groups. The matched cohort included 2,464 patients, with 1,232 in each group. All covariates had SMD < 0.1 after propensity score matching, indicating good baseline balance (**Table 2**).

Outcomes

Kaplan-Meier survival curves for the propensity score-matched cohort showed better survival in the DHP group than in the no-DHP group (30-day: HR, 0.827; *P* = 0.046; 60-day: HR, 0.795; *P* = 0.008; 90-day: HR, 0.782; *P* = 0.003) (**Figure 2**). Primary outcomes were further evaluated using univariate and multivariable-adjusted Cox proportional hazards models in the propensity score-matched cohort (**Figure 3**).

The proportional-hazards (PH) assumption was assessed using the Schoenfeld residual test. The test yielded *P* values of 0.42 for 30-day mortality, 0.82 for 60-day mortality, and 0.75 for 90-day mortality. All *P* values were greater than 0.05, indicating no statistically significant violation of the PH assumption. Thus, the

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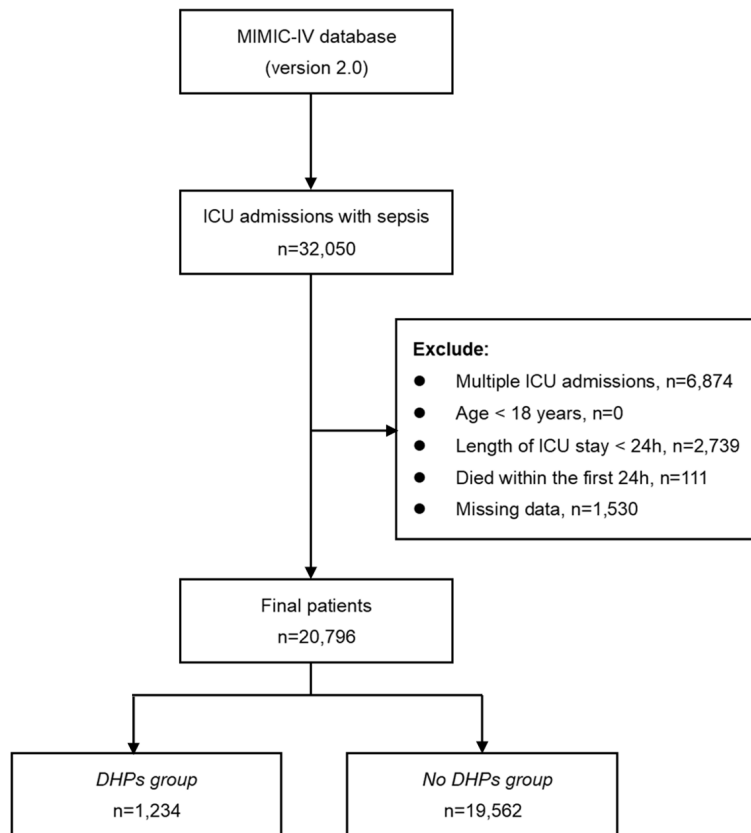


Figure 1. Flow chart of patient selection. MIMIC-IV, Medical Information Mart for Intensive Care IV; ICU, intensive care unit; DHP group, dihydropyridine group, comprising patients who had used dihydropyridine calcium channel blockers within 1 month before ICU admission; no-DHP group, no-dihydropyridine group, comprising patients who had not used dihydropyridine calcium channel blockers within 1 month before ICU admission.

results supported the use of Cox proportional hazards models to evaluate the survival endpoints in this study.

The univariate Cox proportional hazards models showed that prior DHP use was associated with reduced 30-day (HR, 0.826; 95% CI, 0.685-0.997; $P = 0.046$), 60-day (HR, 0.795; 95% CI, 0.670-0.943; $P = 0.008$), and 90-day (HR, 0.782; 95% CI, 0.665-0.919; $P = 0.003$) mortality.

The multivariate-adjusted Cox proportional hazard models showed that prior DHP use was independently associated with reduced 30-day (HR, 0.800; 95% CI, 0.662-0.968; $P = 0.021$), 60-day (HR, 0.776; 95% CI, 0.653-0.922; $P = 0.004$) and 90-day (HR, 0.760; 95% CI, 0.645-0.895; $P = 0.001$) mortality. In addition, higher body temperature (HR, 0.857; 95% CI, 0.765-0.960; $P = 0.008$) and higher Glasgow Coma

Score (GCS) (HR, 0.933; 95% CI, 0.911-0.957; $P < 0.001$) were independently associated with reduced 90-day mortality among patients with sepsis. Factors independently associated with increased 90-day modality included liver disease (HR, 1.478; 95% CI, 1.132-1.930; $P = 0.004$), cancer (HR, 2.887; 95% CI, 2.413-3.455; $P < 0.001$), higher Sequential Organ Failure Assessment (SOFA) score (HR, 1.096; 95% CI, 1.062-1.131; $P < 0.001$), and older age (HR, 1.027; 95% CI, 1.019-1.035; $P < 0.001$) (Figure 4).

There was no significant difference in ICU length of stay between the groups ($P = 0.532$).

Subgroup analysis

To evaluate the association between DHP use and 90-day mortality across different clinically characterized subgroups of patients with sepsis, we performed subgroup analyses (Figure 5). The survival association BETWEEN prior DHP use and improved survival appeared more pronounced among middle-aged (45-64 years) and older (≥ 65 years) men, patients with lower SOFA scores (0-8), and patients with higher Charlson Comorbidity Index scores (≥ 5). A more favorable association was also observed among patients with myocardial infarction, congestive heart failure, renal disease, or diabetes.

Discussion

In this propensity score-matched retrospective cohort study, we investigated the association between prior DHP use and outcomes among patients with sepsis in the ICU. Our findings showed that prior DHP use was associated with improved survival. These findings are consistent with previous clinical studies investigating the relationship between CCB use and sepsis outcomes [16, 17]. However, Kim et al. investi-

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Table 2. Baseline characteristics of sepsis patients before and after matching

Variables	Unmatch cohort			Matched cohort		
	DHPs group n=1,234	No DHPs group n=19,562	SMD	DHPs group n=1,232	No DHPs group n=1,232	SMD
Demographics						
Age (years)	72 (62-80)	67 (56-78)	0.302*	72 (62-80)	72 (62-81)	0.012
Gender, n (%)			0.015			0.036
Male	703 (56.97)	11292 (57.72)		702 (56.98)	724 (58.77)	
Race, n (%)						
Asian	44 (3.57)	545 (2.79)	0.044	44 (3.57)	42 (3.41)	0.008
Black	195 (15.80)	1620 (8.28)	0.232*	193 (15.67)	176 (14.29)	0.038
Hispanic	62 (5.02)	635 (3.25)	0.089	62 (5.03)	69 (5.60)	0.025
White	799 (64.75)	13311 (68.05)	0.069	799 (64.85)	805 (65.34)	0.010
Other/Unknown	134 (10.86)	3451 (17.64)	0.194*	134 (10.88)	140 (11.36)	0.015
Weight (kg)	78.0 (66.1-92.5)	78.7 (65.9-94.0)	0.040	78.0 (66.1-92.6)	77.5 (65.3-92.7)	0.016
Vital signs						
Heart rate (bpm)	99 (88-115)	105 (92-120)	0.219*	99 (88-115)	100 (88-114)	0.018
MAP (mmHg)	57 (51-64)	57 (51-63)	0.034	57 (51-64)	57 (51-63)	0.003
Respiratory rate (insp/min)	28 (24-32)	28 (24-32)	0.018	28 (24-32)	28 (24-32)	0.002
SpO ₂ (%)	92 (90-95)	93 (90-95)	0.041	92 (90-95)	92 (90-95)	0.027
Temperature (°)	37.3 (37.0-37.9)	37.4 (37.0-38.0)	0.050	37.3 (37.0-37.9)	37.3 (36.9-37.9)	0.016
Laboratory results						
Hemoglobin (g/L)	90.0 (78.0-104.0)	97.0 (83.0-112.0)	0.290*	90.0 (78.0-104.0)	90.0 (78.0-103.0)	0.032
Platelet (10 ⁹ /L)	176.5 (126.0-250.0)	160.0 (109.0-226.0)	0.190*	177.0 (126.0-250.0)	174.0 (120.0-245.0)	0.025
WBC (10 ⁹ /L)	13.3 (9.6-18.2)	13.9 (9.9-18.9)	0.056	13.4 (9.6-18.2)	13.4 (9.6-18.2)	0.010
BUN (mg/dL)	27.0 (18.0-45.0)	23.0 (16.0-39.0)	0.159*	27.0 (18.0-45.0)	27.0 (17.0-45.0)	0.003
Serum creatinine (mg/dL)	1.3 (0.9-2.4)	1.1 (0.8-1.8)	0.201*	1.3 (0.9-2.4)	1.3 (0.9-2.2)	<0.001
Glucose (mg/dL)	147.5 (118.0-204.0)	146.0 (118.0-193.0)	0.024	147.0 (118.0-204.0)	147.0 (116.0-201.0)	0.036
Anion gap (mmol/L)	16.0 (13.0-19.0)	16.0 (13.0-19.0)	0.048	16.0 (13.0-19.0)	16.0 (13.0-19.0)	0.013
Bicarbonate (mmol/L)	24.0 (22.0-27.0)	24.0 (22.0-27.0)	0.090	24.0 (22.0-27.0)	25.0 (22.0-27.0)	0.058
Disease severity score						
GCS	14 (10-15)	14 (10-15)	0.051	14 (10-15)	14 (10-15)	0.024
SOFA score	6 (4-8)	6 (4-9)	0.098	6 (4-8)	5 (4-8)	<0.001
Comorbidities, n (%)						
Myocardial infarction	281 (22.77)	3349 (17.12)	0.141*	279 (22.65)	290 (23.54)	0.021
Congestive heart failure	425 (34.44)	5716 (29.22)	0.112*	425 (34.50)	414 (33.60)	0.018
Peripheral vascular disease	210 (17.02)	2184 (11.16)	0.168*	209 (16.96)	211 (17.13)	0.004
Cerebrovascular disease	227 (18.40)	2573 (13.15)	0.144*	226 (18.34)	210 (17.05)	0.034
Chronic pulmonary disease	314 (25.45)	5272 (26.95)	0.034	313 (25.41)	329 (26.70)	0.029
Liver disease	102 (8.27)	3150 (16.10)	0.241*	102 (8.28)	103 (8.36)	0.002
Renal disease	508 (41.17)	4156 (21.25)	0.440*	506 (41.07)	512 (41.56)	0.009
Diabetes	566 (45.87)	5944 (30.39)	0.322*	564 (45.78)	552 (44.81)	0.019
Rheumatic disease	46 (3.73)	721 (3.69)	0.002	46 (3.73)	43 (3.49)	0.013
Peptic ulcer disease	37 (3.00)	636 (3.25)	0.014	37 (3.00)	38 (3.08)	0.004
Dementia	36 (2.92)	899 (4.60)	0.088	36 (2.92)	36 (2.92)	<0.001
Paraplegia	48 (3.89)	859 (4.39)	0.025	48 (3.90)	43 (3.49)	0.021
Cancer	205 (16.61)	3202 (16.37)	0.006	205 (16.64)	199 (16.15)	0.013
AIDS	4 (0.32)	151 (0.77)	0.060	4 (0.32)	4 (0.32)	<0.001

DHP group, dihydropyridine group; no-DHP group, no-dihydropyridine group; MAP, mean arterial pressure; SpO₂, peripheral oxygen saturation; WBC, white blood cell count; BUN, blood urea nitrogen; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; AIDS, acquired immunodeficiency syndrome; SMD, Standardized Mean Difference. *SMD>0.1

gated sepsis-related outcomes across different classes of antihypertensive medications and found that the survival benefit was not prominent among prior CCB users [18].

The association between DHP use and improved survival observed in our study may provide a basis for further investigation of DHPs in the management of sepsis, particularly am-

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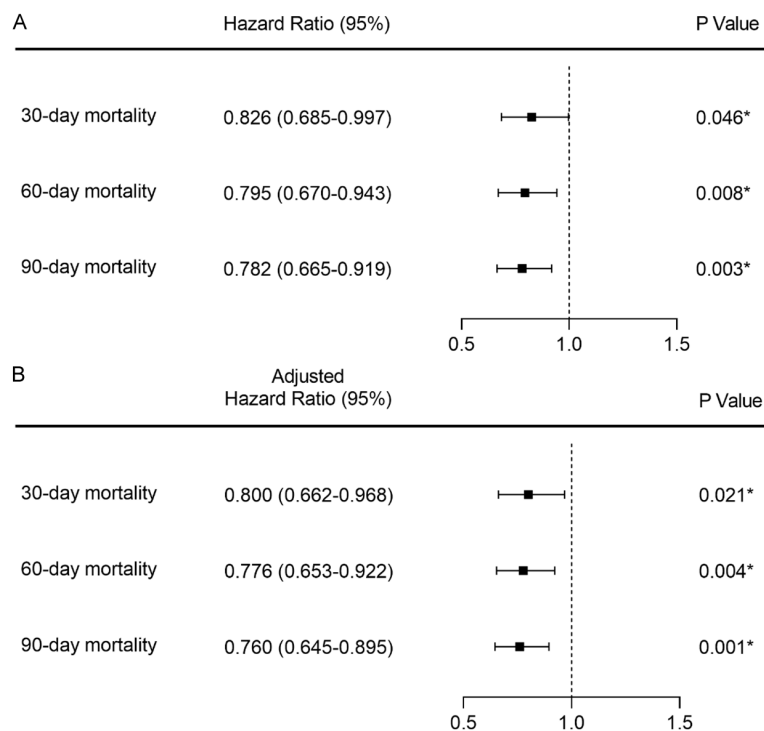
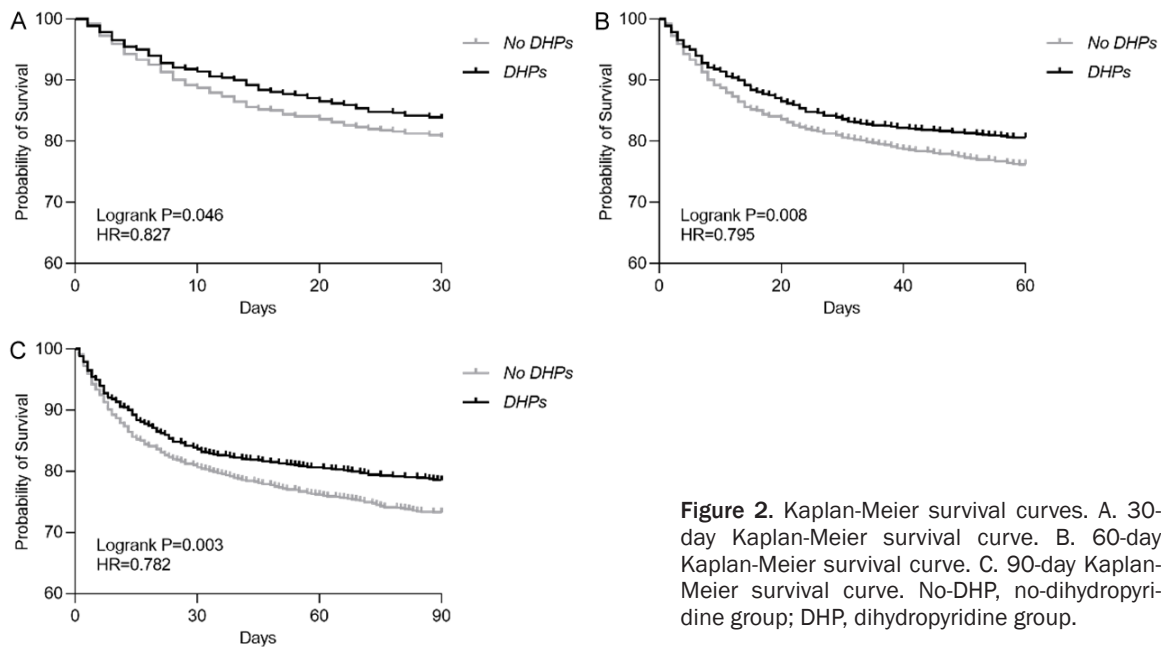


Figure 3. Primary outcomes. Forest plots showing the association between prior DHP use and primary outcomes in patients with sepsis. A. Univariate Cox proportional hazards models. B. Multivariable-adjusted Cox proportional hazards models. * $P < 0.05$.

ong patients with cardiovascular comorbidities such as myocardial infarction and congestive heart failure. This association may be related to the cardiovascular effects of DHPs beyond

their antihypertensive properties. Horiuchi et al. suggested that nifedipine can inhibit the expression of the pro-atherosclerotic monocyte chemoattractant protein-1 (MCP-1) by inhibiting nuclear factor kappa B (NF- κ B) activation, thereby suppressing vascular smooth muscle proliferation and improving vascular remodeling [19]. The protective effect of amlodipine against myocardial injury in congestive heart failure may be associated with inhibition of excessive nitric oxide (NO) production [20]. Interestingly, the survival benefit associated with DHP use was also more pronounced among patients with renal disease or diabetes in our study. The precise mechanisms underlying these associations require further investigation.

Hsu et al. reported intracellular redistribution of DHP receptors in the rat heart during the progression of sepsis, with receptor expression increasing during early sepsis and decreasing during late sepsis [21]. This finding suggests that the

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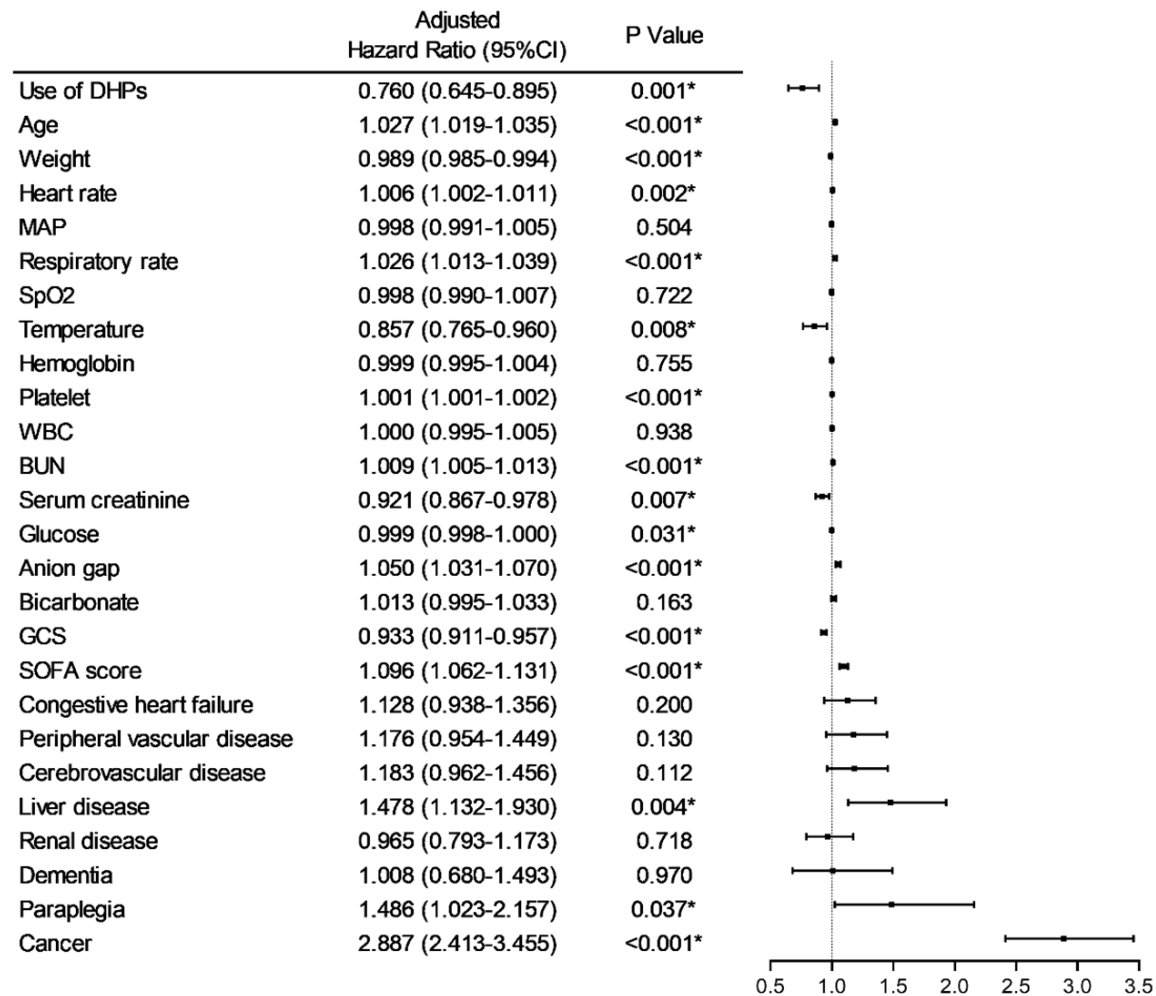


Figure 4. Multivariable-adjusted Cox proportional hazards model of 90-day mortality. DHP, dihydropyridine; MAP, mean arterial pressure; SpO₂, peripheral oxygen saturation; WBC, white blood cell count; BUN, blood urea nitrogen; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment. *P<0.05.

timing of DHP exposure may be important in patients with sepsis. Chen et al. found that nitrosonisoldipine (NTS), a photodegradation product of the dihydropyridine calcium channel blocker nisoldipine, could selectively inhibit inflammatory caspases and block both noncanonical and canonical pyroptotic pathways in septic models [22]. These findings provide further insight into potential mechanisms through which DHPs may exert beneficial effects in sepsis.

This study has several limitations. First, as a retrospective cohort study, it is subject to residual confounding and other biases. Although propensity score matching was used to reduce confounding, bias due to unmeasured confounders cannot be completely excluded. The

survival difference identified in this study may partly reflect a healthy-user effect and differences in chronic disease care, rather than a true pharmacological effect exerted by DHPs themselves. Despite matching on measured baseline covariates, unmeasured confounding continues to represent an important source of residual bias. Second, MIMIC-IV is a single-center database, which may limit the generalizability of our findings. The observed association between DHP use and survival should therefore be validated in external databases and, ideally, prospective studies. Third, the total Charlson Comorbidity Index (CCI) score was not included as a covariate. Instead, individual comorbid conditions that constitute the CCI were incorporated as separate covariates. Concurrent inclusion of both the composite CCI

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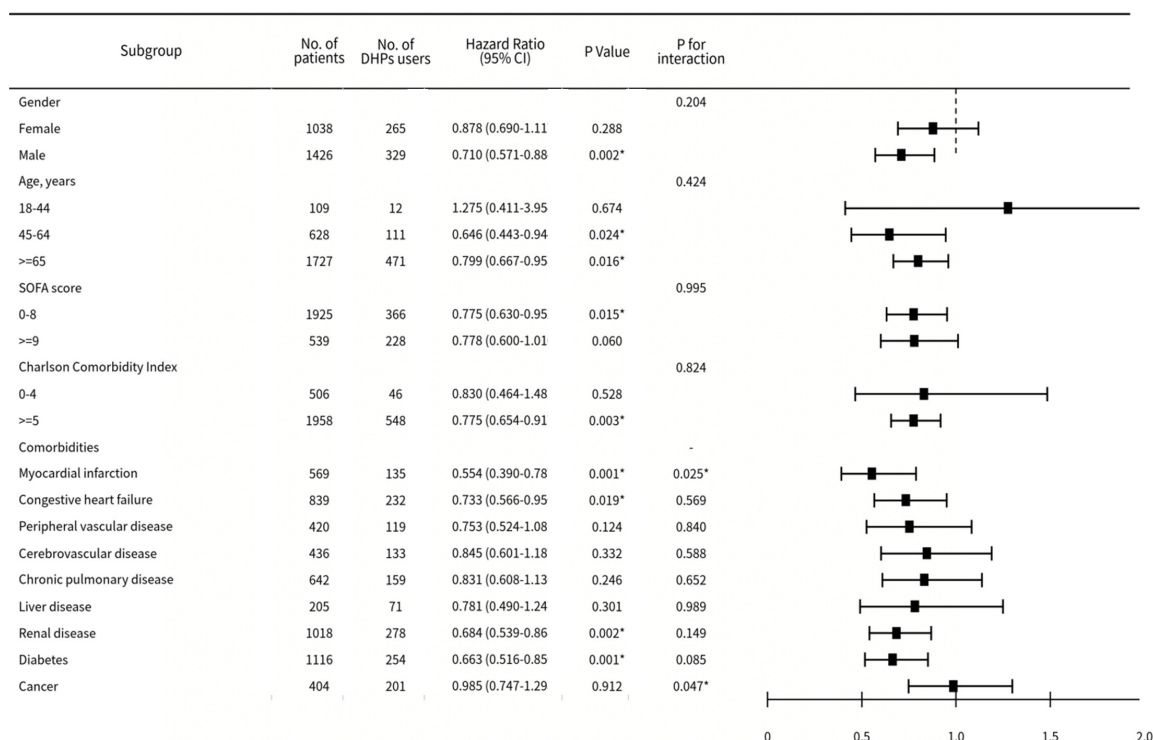


Figure 5. Subgroup analysis. Forest plots showing the association between prior DHP use and 90-day mortality among different subgroups of patients with sepsis. SOFA, Sequential Organ Failure Assessment. *P<0.05.

score and its individual component diseases could introduce multicollinearity. Finally, our study does not establish the underlying mechanisms linking DHP use to mortality in patients with sepsis; elucidating these mechanisms will be an important focus of future research.

Conclusions

Prior use of dihydropyridines was associated with reduced mortality among patients with sepsis in the ICU. The mechanisms underlying this association require further investigation.

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Disclosure of conflict of interest

None.

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