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Dexmedetomidine improves prognosis in septic patients with myocardial injury and lower APACHE IV scores: a retrospective cohort study

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Abstract

Background and objective Sepsis is a major cause of mortality, particularly in patients with myocardial injury. The objective of this study was to evaluate the impact of dexmedetomidine, propofol, and midazolam on mortality and various outcomes in this population.

Methods A retrospective cohort study was performed using the eICU database, encompassing 2,171 septic patients with myocardial injury. Patients were categorized into single- and multiple-sedative groups. The primary endpoint was 100-day mortality, with secondary endpoints encompassing hospital stay, intensive care unit (ICU) stay, mechanical ventilation (MV), and dialysis. Statistical analysis was conducted using Cox regression, Kaplan-Meier curves, and propensity score matching.

Results Among 2,171 patients, dexmedetomidine was associated with lower 100-day mortality in patients with APACHE IV scores < 78.9, particularly in specific subgroups. In patients with APACHE IV scores ≥ 78.9, dexmedetomidine provided no mortality advantage over propofol. Midazolam was linked to higher mortality across all score ranges, and its combination with propofol resulted in worse outcomes compared to dexmedetomidine-propofol. No significant differences were found in hospital stay, ICU stay, or MV rates between the groups.

Conclusion Dexmedetomidine improves prognosis in septic patients with myocardial injury, particularly in those with lower severity of illness, highlighting its potential as a preferred sedative choice in this population.

Keywords Dexmedetomidine, Propofol, Midazolam, Sepsis, Mortality

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Introduction

Sepsis and septic shock remain leading causes of mortality worldwide, placing a significant burden on healthcare systems. Recent global burden estimates indicate substantial variations in mortality rates across different regions and healthcare settings, influenced by disparities in resources, patient populations, and clinical practices [1]. Despite advancements in the management of sepsis, including early recognition and improved supportive care, the condition continues to pose major challenges, particularly in critically ill patients with organ dysfunction. Understanding the complex factors contributing to these outcomes, including sedation strategies, is crucial for improving care in this high-risk population. It is characterized as a complex syndrome resulting from a dysregulated host response to infection, leading to physiological, pathological, and potentially lethal organ dysfunctions [2, 3]. Among the various complications of sepsis, myocardial injury has emerged as a key contributor to poor outcomes, although the precise mechanisms linking sepsis and myocardial depression remain incompletely understood [4]. Elevated levels of biomarkers such as troponin are often used to identify myocardial injury in septic patients, with increasing evidence suggesting that this condition worsens prognosis.

Sedation is a standard intervention in the management of septic patients, particularly those requiring MV in the ICU. The use of sedatives aims to reduce discomfort, alleviate anxiety, facilitate nursing care, and improve ventilator tolerance, while minimizing the risk of accidental dislodgement of essential equipment, such as endotracheal tubes [5]. However, sedative choice in this setting can have profound effects on patient outcomes. Midazolam, a commonly used sedative, has been associated with adverse outcomes, including increased mortality, prolonged MV, and extended ICU stays [6]. A comprehensive analysis of 1,551 ICU patients demonstrated that midazolam use resulted in significantly longer ICU stays and MV times compared to non-benzodiazepine sedatives like propofol and dexmedetomidine [7].

Dexmedetomidine, a selective alpha-2 adrenergic agonist, has garnered attention for its potential protective effects on vital organs, including the heart, kidneys, and brain, particularly in critically ill patients [8]. Despite its benefits, dexmedetomidine is known to induce hypotension and bradycardia, raising concerns about its safety in patients with sepsis-induced myocardial injury [9]. In contrast, propofol, another commonly used sedative, is associated with vasodilation and may exacerbate hypotension in hemodynamically unstable patients. These differences in the cardiovascular effects of sedatives highlight the need for careful consideration when managing septic patients with myocardial injury. Despite the widespread use of these sedatives, there is a lack of comprehensive studies directly comparing their prognostic outcomes in septic patients with myocardial injury. Most existing studies focus on general ICU populations without specific emphasis on myocardial injury, leaving a critical gap in our understanding of optimal sedation strategies in this high-risk group.

This study aims to address this gap by evaluating the prognostic outcomes associated with midazolam, propofol, and dexmedetomidine in septic patients with coexisting myocardial injury. By analyzing real-world data from a large multi-center database, we aim to identify the most suitable sedative therapy to improve mortality, ICU length of stay, and other clinical outcomes in this patient population.

Methods

Ethical declaration

The Ethics Committee of the First Affiliated Hospital of SUN YAT-SEN University (Guangzhou, China) confirmed that ethical approval was not necessary ([2023]057). The need for obtaining informed consent was waived because of the retrospective nature of the study. Human Ethics and Consent to Participate declarations: not applicable. Clinical trial number: not applicable.

Study design

This study is a retrospective observational cohort study utilizing data from multiple centers. The data were sourced from the eICU Collaborative Research Database (2014–2015, available at https://eicu-crd.mit.edu/), which is maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology [10, 11]. The dataset contains de-identified patient records, and authorization to extract data was granted (certification number: 9112715). This retrospective design may introduce selection bias, which we mitigated using propensity score matching (PSM) and multivariable analyses to adjust for potential confounders.

Patient selection

Patients included in this study were those diagnosed with sepsis and myocardial injury, following the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [12]. Myocardial injury was defined based on troponin I or T levels exceeding the threshold of 0.013 ng/mL, indicating cardiac damage [13, 14]. Myocardial injury is a common complication in sepsis, with reported prevalence rates varying between 20 and 60%, depending on the definition and diagnostic criteria. Studies have shown that using biomarkers such as troponin, myocardial injury can be identified in a substantial proportion of septic patients. For instance, Kakihana et al. [15] reported that 20–50% of septic patients exhibited elevated

troponin levels. Similarly, Yang et al. [4] noted that high-sensitivity troponin assays reveal myocardial injury in over 50% of septic patients. In this study, myocardial injury was defined as a troponin I or T level > 0.013 ng/mL, which aligns with thresholds commonly used in the literature for detecting clinically significant myocardial injury. Sedatives analyzed in this study were dexmedetomidine, propofol, and midazolam. Patients younger than 18 years of age were excluded from the analysis. The study population was divided into two main cohorts. The first cohort, the single-sedative group, included patients receiving one of the three sedatives, and comparisons were made between propofol and dexmedetomidine, midazolam and dexmedetomidine, and midazolam and propofol. The second cohort, the multiple-sedative group, focused on combinations of sedatives, such as dexmedetomidine-midazolam versus dexmedetomidine-propofol, dexmedetomidine-midazolam versus propofol-midazolam, and dexmedetomidine-propofol versus propofol-midazolam. Patients were categorized into the midazolam group if midazolam was administered at least once during their ICU stay, regardless of whether it was given as intermittent boluses or continuous infusion. However, due to limitations of the eICU database, we were unable to distinguish between these two modes of administration.

Data collection and outcomes assessment

Patient characteristics were extracted using PostgreSQL (pSQL) and included demographic variables such as age, sex, body weight, height, and ethnicity, as well as clinical and laboratory measurements. Key laboratory values included Brain Natriuretic Peptide (BNP), troponin I and T levels, white blood cell (WBC) counts, and lymphocyte counts. Sedation type, Acute Physiology and Chronic Health Evaluation (APACHE) IV scores, vasopressor use, MV requirement, and renal replacement therapy status were also recorded. Extreme WBC values were extracted according to APACHE IV criteria, and the highest values of BNP and troponin were used for analysis. Comorbidities such as congestive heart failure (CHF), diabetes, hypertension, cirrhosis, malignancy, chronic obstructive pulmonary disease (COPD), chronic respiratory failure, chronic renal failure, and Coronary Heart Disease (CHD) were documented based on hospital records. The primary outcome of the study was 100-day hospital mortality, while secondary outcomes included ICU length of stay, overall hospitalization duration, and the likelihood of requiring MV or dialysis. The primary endpoint of 100-day mortality was chosen to balance the need for capturing short-term outcomes, such as acute responses to sedation, and intermediate-term outcomes that reflect recovery trajectories in septic patients. This time frame aligns with previous studies on critical care populations and provides a comprehensive assessment of patient survival beyond the acute hospitalization period. Sedation protocols varied across centers in the eICU database, reflecting real-world clinical practice. Typically, the initiation of sedative agents was guided by patient condition and clinician judgment, with adjustments made based on hemodynamic stability and ventilator tolerance. Dexmedetomidine was often used for its hemodynamic stability, propofol for rapid induction, and midazolam in specific clinical scenarios. However, standardized protocols for sedation depth or duration were not available in the dataset.

Statistical analysis

All statistical analyses were conducted using the R package version 4.1.1 and GraphPad Prism version 10. Descriptive statistics were calculated for continuous and categorical variables, with continuous variables reported as means with standard deviations (SD), and categorical variables presented as frequencies and percentages. Comparisons between groups were made using Student's t-test for continuous variables and the chi-square test for categorical variables. To evaluate the impact of different sedative regimens on 100-day mortality, the Hazard Ratio (HR) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models. Concurrent use of analgesics, including opioids, was recorded and incorporated as a covariate in the multivariable analyses. This adjustment aimed to account for potential confounding effects of analgesic use on patient outcomes. Fisher's exact test was used for subgroup analyses to explore potential interactions between dexmedetomidine use and mortality in various subpopulations, stratified by age (< 60 or ≥ 60 years), sex (female or male), WBC count (≤ 10 or > 10 × 10^9/L), comorbidities, APACHE IV scores, and ventilation status. Survival outcomes were further assessed through log-rank tests, with stratification based on APACHE IV scores.

To control for confounding variables and baseline differences between treatment groups, propensity score matching (PSM) was employed using a 1:1 ratio. In the propensity score matching process, we included age, weight, ethnicity, and gender as covariates, along with additional clinical factors such as APACHE IV score, comorbidities (e.g., chronic heart failure, chronic renal failure), and key interventions (e.g., mechanical ventilation, vasopressor use). Concurrent use of analgesics, including opioids, was recorded and incorporated as a covariate in the propensity score matching process to balance patient characteristics across sedative groups. Additionally, analgesic use was included as a covariate in the multivariable regression analysis to adjust for its potential influence on clinical outcomes. These additional covariates were selected to account for baseline

severity of illness and treatment intensity, which are critical confounders in the comparison of sedative groups in critically ill patients.PSM was applied to both the single-sedative and multiple-sedative cohorts to ensure balanced comparisons. After matching, Fisher's exact test or the chi-square test was used to evaluate differences in outcomes, and multivariable analyses were performed to account for additional factors. A p-value of less than 0.05 was considered statistically significant for all analyses.

Results

Patient characteristics

A total of 2,171 patients were included in the study. Of these, 438 received dexmedetomidine, 1,598 received propofol, and 658 received midazolam. These patients were further divided into single-sedative groups (152 received dexmedetomidine, 1,121 received propofol, and 365 received midazolam) and multiple-sedative groups (229 received propofol + dexmedetomidine, 41 received midazolam + dexmedetomidine, and 188 received propofol + midazolam). The overall 100-day mortality rate was 26.99%, and the rate of MV was 95.07%. Table 1 provides a detailed breakdown of patient characteristics, stratified by 100-day mortality. The proportion of patients requiring vasopressor support, as well as the mean vasopressor dose and duration, was comparable among the dexmedetomidine, propofol, and midazolam groups, as detailed in Supplementary Table 1. Precise information on the timing and duration of sedative use was not available in the eICU database. This limitation may impact the ability to evaluate dose-response relationships and the temporal effects of sedation strategies on outcomes. Limited data on causes of death were available in the eICU database. Among patients with documented causes of death, the most common were multiorgan failure, refractory septic shock, and respiratory failure. However, for a significant proportion of patients, detailed cause-of-death information was not provided. Supplementary Table 2 presents a comparison of outcomes between patients receiving dexmedetomidine alone versus those receiving a combination of dexmedetomidine and propofol. Outcomes include 100-day mortality rate, proportion of patients requiring vasopressors, mean vasopressor duration, and incidence of renal support.

Cox regression analysis for single-sedative groups

Cox regression analysis identified significant predictors of 100-day mortality. The use of midazolam, advanced age, elevated APACHE IV scores, and the coexistence of hypertension and Coronary Heart Disease (CHD) were significantly associated with increased mortality across the three sedative groups (Table 2). In line with previous studies, we utilized an APACHE IV score threshold of 78.9 to predict mortality risk, with higher scores indicating an elevated likelihood of death [16]. Kaplan-Meier survival curves were constructed to analyze mortality based on this cutoff (Figure S1). Patients with APACHE IV scores below 78.9 exhibited lower mortality rates compared to those with higher scores.

Dexmedetomidine was associated with a significant reduction in 100-day mortality among patients with APACHE IV scores less than 78.9 (Fig. 1A). However, among patients with scores ≥ 78.9, dexmedetomidine provided no mortality advantage over propofol (Fig. 1B). Midazolam, in contrast, demonstrated a strong association with increased mortality across all APACHE IV score ranges, irrespective of the severity of illness (Fig. 1).

Subgroup analysis for single-sedative groups

A stratified analysis further revealed that dexmedetomidine may reduce 100-day mortality in specific subgroups. Elderly patients (≥ 60 years) who received dexmedetomidine had a significantly lower risk of death (OR 0.54, 95% CI: 0.31–0.89, $p < 0.01$). The mortality benefit of dexmedetomidine was also observed in males (OR 0.39, 95% CI: 0.19–0.74, $p < 0.0001$), patients with WBC counts ≥ 10 K/uL (OR 0.52, 95% CI: 0.31–0.84, $p < 0.001$), those with APACHE IV scores < 78.9 (OR 0.13, 95% CI: 0.01–0.49, $p < 0.001$), non-ventilated patients (OR 0.22, 95% CI: 0.06–0.69, $p < 0.01$), and patients without hypertension (OR 0.46, 95% CI: 0.23–0.86, $p < 0.01$) or CHD (OR 0.47, 95% CI: 0.26–0.81, $p < 0.001$) (Fig. 2).

Additional subgroup analyses were conducted based on sepsis severity, as stratified by APACHE IV scores. Patients with scores below 78.9 demonstrated significant survival benefits with dexmedetomidine compared to propofol or midazolam. In contrast, for patients with scores of 78.9 or higher, the differences in mortality between sedation groups were not statistically significant. These findings are summarized in Supplementary Table 3.

Multivariable analysis before and after propensity score matching (PSM) for single-sedative group

A multivariable analysis was performed for the single-sedative groups after 1:1 PSM. A cohort of 144 patients receiving dexmedetomidine was matched with non-dexmedetomidine patients. The results indicated that dexmedetomidine-treated patients had lower 100-day mortality compared to those receiving midazolam or propofol. Dexmedetomidine also appeared to reduce the need for ventilator support and norepinephrine use. After PSM, dexmedetomidine patients showed a higher incidence of dialysis compared to the midazolam group, while propofol and midazolam groups had a higher proportion of patients requiring MV compared to the dexmedetomidine group. There were no significant

Table 1 Comparisons of the clinical characteristics stratified by mortality

Characteristics	*N* = 2171	Survival *N* = 1585	Mortality *N* = 586	*p* value
Age (mean (SD))	64.86 (14.00)	63.97 (14.31)	67.31 (12.80)	< 0.001
BNP pg/ml (mean (SD))	5973.17 (13668.52)	5788.88 (13520.08)	6553.00 (14150.27)	0.525
Troponin I ng/ml (mean (SD))	4.19 (21.03)	3.00 (16.52)	7.16 (29.19)	< 0.001
Troponin T ng/ml (mean (SD))	0.50 (2.25)	0.59 (2.67)	0.31 (0.68)	0.447
WBC counts (mean (SD))	19.83 (12.69)	19.00 (10.74)	22.07 (16.69)	< 0.001
CHF, n (%)	398 (18.3)	290 (18.3)	108 (18.4)	0.993
Diabetes, n (%)	736 (33.9)	540 (34.1)	196 (33.4)	0.825
Hypertension, n (%)	1123 (51.7)	834 (52.6)	289 (49.3)	0.188
COPD, n(%)	425 (19.6)	301 (19.0)	124 (21.2)	0.285
Cirrhosis, n (%)	110 (5.1)	58 (3.7)	52 (8.9)	< 0.001
Tumor, n (%)	341 (15.7)	213 (13.4)	128 (21.8)	< 0.001
Chronic Respiratory Failure, , n (%)	52 (2.4)	33 (2.1)	19 (3.2)	0.158
CHD, n (%)	420 (19.3)	278 (17.5)	142 (24.2)	0.001
Chronic Renal Failure, n (%)	229 (10.5)	155 (9.8)	74 (12.6)	0.066
Dialysis, n (%)	603 (27.8)	456 (28.8)	147 (25.1)	0.099
Ventilation proportion, n (%)	2064 (95.1)	1499 (94.6)	565 (96.4)	0.099
Weight (mean (SD))	85.11 (28.86)	85.84 (28.81)	83.11 (28.95)	0.051
Height (mean (SD))	169.43 (12.25)	169.55 (12.06)	169.11 (12.74)	0.457
Ethnicity, n (%)				0.809
African American	150 (6.9)	114 (7.2)	36 (6.1)	
Asian	26 (1.2)	19 (1.2)	7 (1.2)	
Caucasian	1718 (79.1)	1247 (78.7)	471 (80.4)	
Hispanic	139 (6.4)	105 (6.6)	34 (5.8)	
Native American	19 (0.9)	12 (0.8)	7 (1.2)	
Other/Unknown	119 (5.5)	88 (5.6)	31 (5.3)	
Acute Physiology score (mean (SD))	74.24 (29.47)	69.43 (26.18)	87.25 (33.68)	< 0.001
APACHE IV score (mean (SD))	87.38 (30.64)	81.87 (27.31)	102.27 (34.04)	< 0.001
Dexmedetomidine, n (%)	438 (20.2)	363 (22.9)	75 (12.8)	< 0.001
Propofol, n (%)	1598 (73.6)	1203 (75.9)	395 (67.4)	< 0.001
Midazolam, n (%)	658 (30.3)	420 (26.5)	238 (40.6)	< 0.001
Lymphocyte (mean (SD))	9.33 (10.41)	9.49 (10.04)	8.87 (11.46)	0.292
Sex = Male, n (%)	1213 (55.9)	876 (55.3)	337 (57.5)	0.376
Norepinephrine, n (%)	1300 (59.88)	813 (51.29)	487 (83.1)	< 0.001
Dopamine, n (%)	129 (6.0)	67 (4.2)	62 (10.7)	< 0.001
Dobutamine, n (%)	113 (5.2)	63 (4.0)	50 (8.6)	< 0.001
Dex + Pro, n (%)	233 (10.7)	197 (12.4)	36 (6.1)	< 0.001
Dex + Mid, n (%)	53 (2.4)	40 (2.5)	13 (2.2)	0.801
Pro + Mid, n (%)	238 (11.0)	165 (10.4)	73 (12.5)	0.201

Dex, Dexmedetomidine; Mid, Midazolam; Pro, Propofol

differences between the groups regarding length of ICU stay or hospitalization (Table 3).

Multivariable analysis before and after PSM for multiple-sedative group

In the multiple-sedative group, PSM was used to match 229 patients receiving dexmedetomidine + propofol with 229 patients who did not receive this combination. The multivariable analysis before and after PSM indicated that the dexmedetomidine + propofol combination was associated with a reduced 100-day mortality rate compared to the propofol + midazolam group. However, this combination also showed an increased likelihood of requiring dialysis when compared to the other two combinations (dexmedetomidine + midazolam and propofol + midazolam). No statistically significant differences were found in MV status, norepinephrine use, ICU length of stay, or hospitalization duration (Table 4).

Table 2 Cox Regression Analysis for single-sedative groups (hazard Ratio[HR] with 95% CI)

Characteristic	Hazard Ratio	95% CI	*p*-value
APACHE IV score	1.019	1.015, 1.022	< 0.001
Age	1.011	1.003, 1.019	0.009
Gender			
Female	—	—	
Male	0.986	0.811, 1.198	0.9
Weight	1	0.996, 1.004	0.9
Ethnicity			
African American	0.107	0.013, 0.855	0.035
Asian	0.131	0.015, 1.169	0.069
Caucasian	0.126	0.016, 0.974	0.047
Hispanic	0.12	0.015, 0.953	0.045
Native American	0.174	0.020, 1.527	0.11
Other/Unknown	0.114	0.014, 0.911	0.041
Comorbidities			
Congestive Heart Failure	0.978	0.759, 1.260	0.9
Diabetes	0.827	0.665, 1.027	0.085
Hypertension	0.789	0.646, 0.964	0.021
COPD	1.051	0.823, 1.341	0.7
Cirrhosis	1.147	0.806, 1.632	0.4
Tumor	1.238	0.982, 1.563	0.071
Chronic Respiratory Failure	1.569	0.891, 2.763	0.12
CHD	1.468	1.170, 1.842	< 0.001
Chronic Renal Failure	0.968	0.717, 1.307	0.8
Treatments			
Dexmedetomidine	—	—	
Midazolam	2.161	1.395, 3.347	< 0.001
Propofol	1.509	0.992, 2.295	0.055

The p-values indicate the statistical significance, with p-values < 0.05 considered significant. HR, Hazard Ratio; CI, Confidence Interval; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; COPD, Chronic Obstructive Pulmonary Disease; and CHD, Coronary Heart Disease

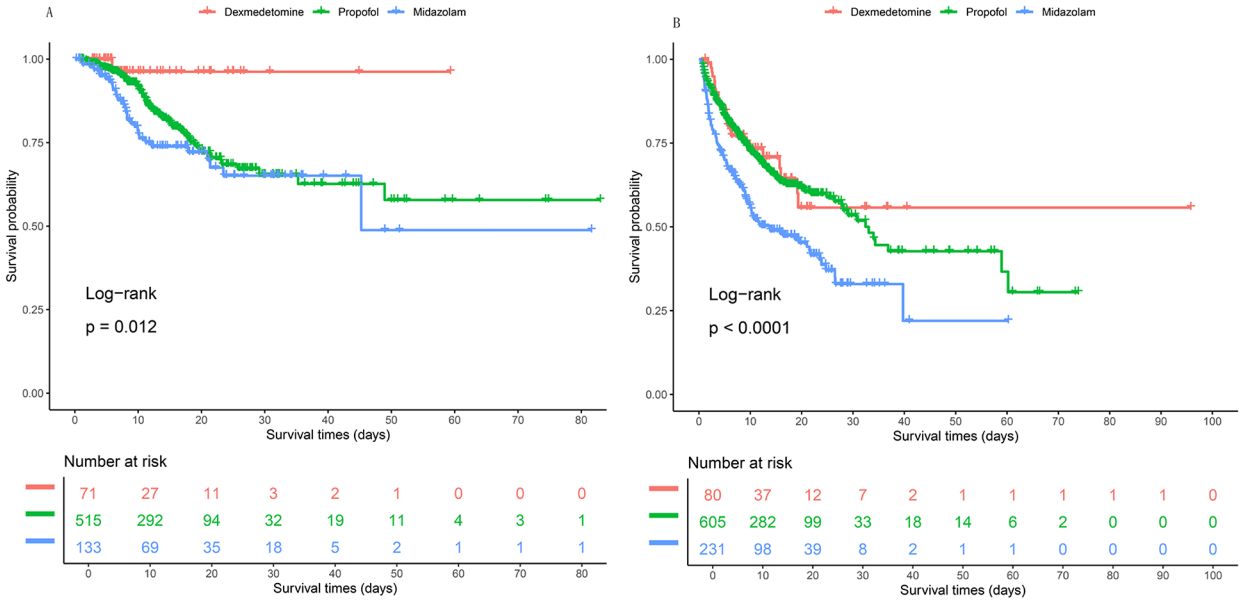

Fig. 1 Kaplan-Meier Estimates of 100-Day mortality in sepsis patients with myocardial impairment, stratified by sedation type and APACHE IV score. Patients receiving multiple sedatives were excluded from the Kaplan-Meier analysis. (**A**) 100-day mortality in patients with APACHE IV scores below 78.9. (**B**) 100-day mortality in patients with APACHE IV scores of 78.9 or higher

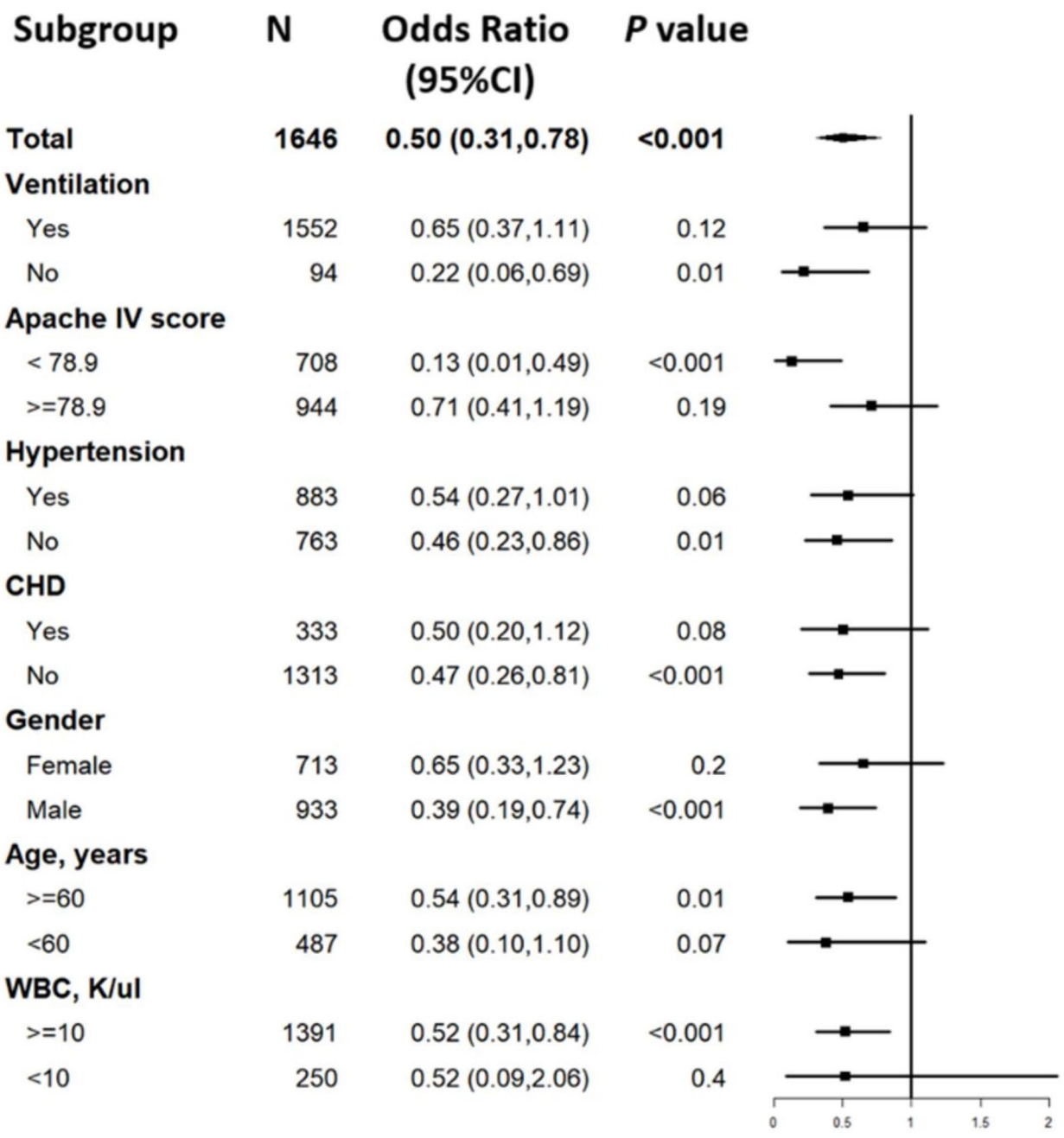

Fig. 2 Subgroup analysis of the association between dexmedetomidine use and mortality in sepsis patients. This figure presents a subgroup analysis examining the association between dexmedetomidine use and mortality in sepsis patients, stratified by various clinical characteristics. CHD, coronary heart disease

Discussion

This study found that dexmedetomidine was associated with lower 100-day mortality in septic patients with myocardial injury, particularly in those with lower APACHE IV scores (<78.9). In contrast, midazolam was linked to the highest mortality across all severity levels. Dexmedetomidine also reduced the need for MV and norepinephrine use, but was associated with a higher incidence of dialysis. In the multiple-sedative group, combining dexmedetomidine with propofol led to lower mortality compared to the propofol-midazolam combination, though with an increased need for dialysis. No

Table 3 Multivariable analysis before and after propensity score matching (PSM) for single-Sedative Group

	Before PSM			After PSM		
	Mid vs. Dex	Pro vs. Dex	Pro vs. Mid	Mid vs. Dex	Pro vs. Dex	Pro vs. Mid
Hospital mortality [a]	3.42 (2.11–5.71), < 0.001	1.65 (1.05–2.68), 0.027	0.48 (0.37–0.62), < 0.001	2.45 (1.06–5.57),0.022	3.72 (2.00-7.02), < 0.001	1.51 (0.69–3.44),0.278
Dialysis Proportion	0.45 (0.30–0.69), < 0.001	0.46 (0.32–0.67), < 0.001	1.02 (0.77–1.36), 0.889	0.44 (0.18–0.99),0.048	0.80 (0.45–1.40),0.424	1.82 (0.77–4.64),0.174
MV Proportion	12.54 (6.98–23.40), < 0.001	58.51 (30.45-120.66), < 0.001	4.67 (2.16–10.40), < 0.001	27.08 (4.34-1119.08), < 0.001	62.43 (10.27-2523.43), < 0.001	2.29 (0.03-182.25),0.519
ICU_ Duration [b]	1.65 (-0.31-3.62),0.119	2.12 (0.35–3.88),0.014	0.46 (-0.76-1.69),0.649	3.53 (1.03–6.03),0.003	1.51 (-0.38-3.39),0.145	-2.02 (-4.64-0.60),0.166
Hospital Duration [b]	0.93 (-2.11-3.96),0.754	1.58 (-1.14-4.29),0.362	0.65 (-1.24-2.54),0.698	3.51 (-1.45-8.48),0.220	-0.62 (-4.37-3.14),0.921	-4.13 (-9.34-1.08),0.151
Norepinephrine Proportion	66.83 (21.05-338.36) < 0.001	50.10 (23.77-118.43) < 0.001	None	-	-	-

Dex, Dexmedetomidine; MV, mechanical ventilation; Mid, Midazolam; Pro, Propofol

a Data are presented as odds ratio (95% confidence interval), *P*-value

b Data are presented as the difference of variable value (95% confidence interval), *P*-value

Table 4 Multivariable analysis before and after PSM for multiple-Sedative Group

	Before PSM			After PSM		
	Dex + Pro vs. Dex + Mid	Pro + Mid vs. Dex + Mid	Pro + Mid vs. Dex + Pro	Dex + Pro vs. Dex + Mid	Pro + Mid vs. Dex + Mid	Pro + Mid vs. Dex + Pro
Hospital mortality [a]	0.56 (0.26–1.26),0.155	1.35 (0.66–2.93),0.411	2.40 (1.50–3.89), < 0.001	0.62 (0.26–1.61),0.252	1.62 (0.70–4.12),0.263	2.62 (1.59–4.37), < 0.001
Dialysis Proportion [a]	2.14 (1.04–4.73),0.038	1.44 (0.69–3.20),0.40	0.67 (0.45-1.00),0.042	2.57 (1.10–6.73),0.021	1.66 (0.69–4.43),0.252	0.65 (0.42-1.00),0.039
MV Proportion [a]	1.78 (0.17–11.28),0.617	1.52 (0.15–8.82),0.640	0.85 (0.20–3.40),1.000	2.29 (0.21–14.59),0.288	1.87 (0.17–11.95),0.612	0.82 (0.19–3.61),0.760
Norepinephrine Proportion [a]	1.02 (0.51–1.98)1.000	1.25 (0.62–2.45)0.509	1.23 (0.82–1.86)0.320	1.14 (0.53–2.38)0.723	1.23 (0.56–2.62)0.585	1.08 (0.70–1.67)0.754
ICU_ Duration [b]	-1.17(-4.18-1.84),0.632	-1.05(-4.05-1.95),0.691	0.12(-1.70-1.94),0.987	-3.04(-6.40-0.33),0.087	-3.11(-6.53-0.31),0.083	-0.07(-2.03-1.88),0.996
Hospital Duration [b]	0.12(-6.22-6.45),0.999	-0.58(-6.90-5.73),0.974	-0.70(-4.53-3.13),0.903	-2.27(-7.57-3.03),0.572	-4.57(-9.95-0.81),0.114	-2.30(-5.37-0.78),0.185

a Data are presented as odds ratio (95% confidence interval), *P*-value

b Data are presented as the difference of variable value (95% confidence interval), *P*-value

Dex, Dexmedetomidine; MV, mechanical ventilation; Mid, Midazolam; Pro, Propofol

significant differences were observed in ICU length of stay or overall hospitalization duration across groups.

Our findings are consistent with previous studies that have questioned the efficacy of dexmedetomidine in certain populations [6, 17]. However, we found that dexmedetomidine was associated with reduced mortality in septic patients with myocardial injury, particularly those with APACHE IV scores below 78.9. This supports prior research suggesting dexmedetomidine's protective effects on key organs, including the heart, kidneys, and

brain, particularly in critically ill patients [8]. For patients with higher APACHE IV scores (≥78.9), dexmedetomidine did not offer a significant survival advantage over propofol, which aligns with previous randomized trials showing no major differences in outcomes between these two sedatives [18].

Midazolam, in contrast, was linked to the highest mortality rates across all APACHE IV score ranges in our study, a finding that aligns with earlier studies demonstrating that midazolam is associated with prolonged MV, extended ICU stays, and worse outcomes compared to non-benzodiazepine sedatives [6, 7]. Midazolam's negative effects on diaphragmatic function and cardiac performance, as well as its weaker antioxidant properties compared to dexmedetomidine and propofol, may explain its association with higher mortality [19]. While propofol has shown protective effects against cardiac injury in preclinical models [20], its vasodilatory properties may contribute to hypotension and bradycardia in septic patients with myocardial injury, which could explain why it did not significantly outperform dexmedetomidine in our study [20, 21]. Overall, these findings reinforce the importance of careful sedative selection in managing septic patients with myocardial injury, particularly in choosing between midazolam, propofol, and dexmedetomidine based on the patient's clinical condition.

The different outcomes observed with dexmedetomidine, propofol, and midazolam can be attributed to their distinct pharmacological mechanisms. Dexmedetomidine, a selective alpha-2 adrenergic agonist, has been noted for its sedative, analgesic, and anti-anxiety properties, while maintaining respiratory stability, which is particularly beneficial for critically ill patients [22, 23]. Although dexmedetomidine can induce hypotension and bradycardia due to its vasodilatory effects, these adverse events are generally dose-dependent [20]. Furthermore, studies have demonstrated that dexmedetomidine does not negatively affect oxygen saturation or carbon dioxide pressure, making it a safer option for patients requiring MV [24]. Its association with shorter extubation times compared to propofol and midazolam also suggests a potential advantage in terms of reducing MV duration [25]. Propofol, a GABA agonist, is widely used in ICUs for its sedative and hypnotic effects. It also possesses vasorelaxant properties, which may contribute to hypotension, bradycardia, and respiratory depression, especially in hemodynamically unstable patients [20, 21]. Despite its protective effects against cardiac injury in preclinical models [20], these vasodilatory effects may limit its use in patients with sepsis-induced myocardial injury. Our findings, where propofol did not significantly outperform dexmedetomidine in patients with higher APACHE IV scores, align with these considerations. Midazolam, a benzodiazepine, was associated with the highest mortality rates in our study. Its negative impact on diaphragmatic function during MV, along with its tendency to impair cardiovascular function, particularly early diastolic filling of the left ventricle, may explain the worse outcomes observed [19, 26]. Additionally, midazolam has weaker antioxidant capacity compared to both dexmedetomidine and propofol, which may contribute to its deleterious effects on critically ill patients [19]. Based on these findings, midazolam should be used cautiously in septic patients, especially those with pre-existing cardiovascular dysfunction.

Dexmedetomidine was associated with a significant reduction in 100-day mortality among patients with APACHE IV scores less than 78.9. However, among patients with scores ≥78.9, dexmedetomidine provided no mortality advantage over propofol. Dexmedetomidine's benefits in patients with lower APACHE IV scores (<78.9) may be attributed to several potential mechanisms. First, as a selective α2-adrenergic agonist, dexmedetomidine stabilizes hemodynamics by reducing sympathetic tone, which may protect against cardiac and vascular stress in less severely ill patients. Second, it has been shown to reduce systemic inflammation and mitigate cytokine release, processes that are less overwhelming in patients with lower disease severity. Third, dexmedetomidine exerts antioxidant and anti-apoptotic effects, which may preserve organ function and improve recovery trajectories in patients with relatively intact physiological reserves [27–29]. These mechanisms are particularly advantageous in patients with lower APACHE scores, where compensatory mechanisms are still functional, and the benefits of dexmedetomidine can be maximized. However, in patients with higher APACHE scores, where critical organ dysfunction is more advanced, the marginal benefits of these mechanisms may be attenuated.

Dexmedetomidine-treated patients in this study showed a higher incidence of dialysis compared to the midazolam group, raising important questions about its potential impact on renal function. One possible explanation lies in the hemodynamic effects of dexmedetomidine, such as bradycardia and hypotension, which may reduce renal perfusion, particularly in hemodynamically unstable patients. This reduction in renal perfusion could exacerbate existing renal dysfunction or precipitate acute kidney injury, necessitating dialysis [30, 31]. Furthermore, patients in the dexmedetomidine group had a higher prevalence of chronic renal failure and other comorbidities, which may have independently contributed to the observed higher dialysis rates, despite adjustment using propensity score matching. It is also possible that institutional or clinician thresholds for initiating dialysis varied, influencing the outcomes observed. Lastly, residual confounding factors not fully captured in the dataset

cannot be excluded. These findings underscore the need for further studies with more detailed hemodynamic and renal function data to better understand the relationship between dexmedetomidine use and renal outcomes, particularly in critically ill patients with pre-existing renal impairment.This study underscores the need for tailored sedative choices in septic patients with myocardial injury. Dexmedetomidine showed a clear survival benefit in patients with lower APACHE IV scores (< 78.9), suggesting it may be particularly useful in less critically ill patients due to its ability to maintain hemodynamic stability and reduce the need for MV and norepinephrine [8]. However, its association with increased dialysis warrants close monitoring in patients with renal concerns. In more severely ill patients (APACHE IV scores ≥ 78.9), dexmedetomidine and propofol showed comparable outcomes, though propofol's vasodilatory effects could be problematic in unstable patients [20, 21]. Midazolam, linked to the highest mortality across all severity levels, should be used cautiously, particularly in patients with cardiac dysfunction due to its adverse effects on respiratory and cardiovascular function [19, 26]. The combination of dexmedetomidine and propofol offered better survival than propofol-midazolam, suggesting that minimizing cardiovascular stress from sedatives may improve outcomes in high-risk patients. Clinically, these findings support using dexmedetomidine, either alone or with propofol, in appropriate cases, while limiting midazolam use in critically ill patients.

The choice of sedatives in this study was guided by attending intensivists based on clinical judgment and patient-specific factors. While detailed documentation of the rationale behind these decisions was unavailable, certain patterns can be inferred from the pharmacological properties of each sedative. For monotherapy, dexmedetomidine was likely selected for its hemodynamic stability and arousability, propofol for its rapid induction and deeper sedation, and midazolam for its lesser hemodynamic effects. For combination therapy, dexmedetomidine and propofol may have been chosen to exploit their synergistic effects, reducing the required dose of each and mitigating adverse effects. Meanwhile, combinations involving midazolam were likely employed in patients with significant hemodynamic compromise or when prolonged sedation was required.

This study's retrospective design inherently introduces potential biases, including selection bias, despite efforts to mitigate these through propensity score matching (PSM) and multivariable analyses. Additionally, the absence of standardized sedation protocols and depth of sedation assessments in the eICU database likely contributed to variability in patient management, which may have influenced the observed outcomes. The lack of detailed information on sedative dosing and duration further restricts our ability to evaluate dose-response relationships and their potential impact on mortality and other clinical endpoints. Missing data on key factors such as vasopressor use and the duration of mechanical ventilation also limit the comprehensiveness of our analysis. Furthermore, the use of a single-country database (eICU Collaborative Research Database), predominantly encompassing a U.S.-based population, restricts the generalizability of these findings to healthcare settings with different patient populations, clinical practices, and resource availability. It is worth noting that patients receiving dexmedetomidine in this study generally presented with less severe illness, which may have contributed to the observed differences in mortality. To strengthen these findings, future research should focus on prospective randomized controlled trials to minimize bias and provide more definitive evidence. Such studies should also aim to include detailed data on sedative dosages, timing of administration relative to sepsis onset, and organ-specific impacts, particularly on renal function. Moreover, expanding the scope to diverse international populations will enhance the generalizability and clinical relevance of these results, enabling the determination of optimal sedation strategies for critically ill patients. This study highlights the need for more detailed investigations into the impact of myocardial injury severity on sedative choice and patient outcomes. Future prospective studies should aim to: Incorporate granular data on troponin levels, catecholamine dosages, and other hemodynamic parameters to better account for the variability in myocardial impairment. Assess the interplay between myocardial injury severity and sedative pharmacodynamics in a controlled setting. Expand the scope to include diverse patient populations and international healthcare settings to enhance generalizability.

In conclusion, this study highlights the distinct outcomes associated with different sedatives in septic patients with myocardial injury. Dexmedetomidine was linked to lower mortality, particularly in less critically ill patients, while midazolam was consistently associated with higher mortality across all severity levels. Propofol showed comparable outcomes to dexmedetomidine in more severe cases but carries its own risks related to hemodynamic stability. These findings suggest that careful selection of sedatives, considering both patient condition and potential side effects, is crucial in improving outcomes for this vulnerable population. Further research is needed to validate these results and optimize sedation strategies in septic patients with myocardial injury.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Not Applicable.

Author contributions
XD conceived the study, collected and analyzed the data, and was a major contributor to the manuscript. DZZ, HL, YLY, and CYZ collected data. HYW reviewed the raw data. CLH conceived of the study and revised the manuscript with JC. XD and HYW contributed equally to this work. All the authors have composed and approved the final manuscript.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of SUN YAT-SEN University (Guangzhou, China) and adhered to the ethical principles outlined in the Declaration of Helsinki. Informed consent forms were obtained from all patients.

Consent for publication
The patient provided written informed consent for publication.

Competing interests
The authors declare no competing interests.

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