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Exploring the impact of dexmedetomidine on short-term outcomes in critically ill sepsis-associated encephalopathy patients

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Abstract. – OBJECTIVE: Dexmedetomidine has demonstrated potential in preclinical medical research as a protective agent against inflammatory injuries and a provider of neuroprotective benefits. However, its effect on the short-term prognosis of patients with sepsis-associated encephalopathy remains unclear. This study aims to explore the underlying value of dexmedetomidine in these patients.

PATIENTS AND METHODS: This study enrolled patients with sepsis-associated encephalopathy from the Medical Information Mart for Intensive Care (MIMIC)-IV database, and they were divided into two groups based on dexmedetomidine therapy during hospitalization. Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) were utilized to balance the inter-group baseline differences. Kaplan-Meier (KM) curves with log-rank test and subgroup analysis were also employed. The primary outcome was 28-day mortality, and the secondary outcomes were in-hospital mortality, intensive care unit (ICU) stay time, hospital stay time, and the incidence of ventilator-associated pneumonia (VAP).

RESULTS: After PSM, 1,075 pairs of patients were matched. In contrast to the non-dexmedetomidine cohort, the dexmedetomidine cohort did not exhibit a shortened ICU [4.65 (3.16, 8.55) *vs.* 6.14 (3.66, 11.04), $p<0.001$] and hospital stay duration [10.04 (6.55, 15.93) *vs.* 12.76 (7.92, 19.95), $p<0.001$], and there was an elevated incidence of VAP [90 (8.4%) *vs.* 135 (12.6%), $p=0.002$]. The log-rank test for the KM curves of dexmedetomidine use and 28-day mortality was statistically significant ($p<0.001$). The results showed that dexmedetomidine was associated with improved 28-day mortality [hazard ratio (HR) 0.46, 95% confidence interval (CI) 0.35-0.61, $p<0.001$] and in-hospital mortality (HR 0.50, 95% CI 0.37-0.67, $p<0.001$) after adjusting for various confounders. In the following subgroup analysis, dexmedetomidine infusion was associated with decreased 28-day mortality in most subgroups.

CONCLUSIONS: Dexmedetomidine administration was significantly associated with reduced short-term mortality among patients with sepsis-associated encephalopathy in the ICU. However, it also prolonged ICU and hospital stays and increased the incidence of VAP.

Key Words:
Dexmedetomidine, Sepsis-associated encephalopathy, Prognosis, Critical care, Propensity score matching.

Introduction

Sepsis, a complex syndrome characterized by an overactive immune response to infection, can lead to organ dysfunction and failure, resulting in fatal outcomes[1]. Mitigating the mortality caused by sepsis is an imperative public health priority on a global scale[2]. The brain is one of the organs primarily affected by the detrimental effects of sepsis, and the central nervous system (CNS) is particularly vulnerable to inflammation and oxidative damage, making it the first to show signs of functional impairment, leading to sepsis-associated encephalopathy (SAE). It has been reported that up to one-third of septic patients in the intensive care unit (ICU) may experience this grim condition, posing a risk factor for long-term disability and mortality rates varying from 16% to 65%[3]. Sepsis-associated encephalopathy (SAE) is defined as a state of diffuse cerebral dysfunction that stems from an aberrant host response in the absence of a central nervous system infection[4]. It manifests in various clinical symptoms, ranging from mild confusion and delirium to profound cognitive impairment and even a deep comatose state[5].

The systemic inflammatory response triggered by sepsis compromises the integrity of the

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blood-brain barrier (BBB), facilitating the entry of peripheral immune cells into the brain and the release of a cascade of inflammatory mediators, leading to uncontrolled neuroinflammation and, ultimately, causing brain dysfunction[6]. Dexmedetomidine (DEX), a highly selective α2-adrenergic receptor agonist drug commonly used in ICUs, is known for its mild sedative effects and has been found to exhibit anti-inflammatory properties, reducing neuroinflammation and BBB impairment in septic mice[7]. Researchers have found that dexmedetomidine can alleviate neuronal pyroptosis (a pro-inflammatory form of cell death characterized by the release of inflammatory mediators during cell death, leading to an inflammatory response in the body), thereby safeguarding brain and ultimately improving the outcomes of sepsis[8,9].

Nonetheless, the value of dexmedetomidine in SAE patients remains insufficiently studied. Literature on its efficacy in SAE patients mostly consists of basic research, lacking comprehensive clinical studies on a large population. Furthermore, despite the widespread administration of dexmedetomidine in ICU patients, its therapeutic effects continue to be a subject of debate. According to a meta-analysis[10], the results indicated that dexmedetomidine did not lead to a decrease in all-cause mortality among mechanically ventilated patients with sepsis. Likewise, in a randomized clinical trial, the administration of dexmedetomidine did not yield a statistically significant improvement in mortality when compared to the absence of dexmedetomidine (p=0.200)[11]. Conversely, a nationwide retrospective cohort study in Japan found a correlation between the use of dexmedetomidine and a lower all-cause mortality rate at 28 days[12]. Therefore, significant attention is warranted in exploring dexmedetomidine therapy in critically ill patients with sepsis.

This research aimed to assess the association between dexmedetomidine administration and short-term outcomes in critically ill patients with sepsis-associated encephalopathy, utilizing data derived from the Medical Information Mart for Intensive Care (MIMIC) IV database. It will provide valuable insights for guiding rational medication use to enhance the prognosis of SAE patients.

Patients and Methods

Data Source

We conducted a retrospective cohort study using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, which integrates detailed patient data from individuals admitted to the Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2008 to 2019. Patients' identifiers were removed to protect their privacy. One author (Jia Tang) obtained full access to the database and was responsible for data extraction (record ID: 52759164). Informed consent was not required as the data were obtained from publicly available sources, and all relevant information was anonymized. This study adhered to the Declaration of Helsinki (as revised in 2013) and the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology. All data were collected prior to the 2019 outbreak of coronavirus disease and extracted in the Structured Query Language (SQL) with PostgreSQL (version 14.7).

Study Population

This study included 4,349 records of critically ill patients with sepsis-associated encephalopathy (SAE) in the MIMIC-IV database from 2008 to 2019. For patients who had hospitalization or ICU admission more than once, only data on the first ICU admission of the first hospitalization was included. Participants were not underage, and only patients with a minimum ICU duration of 2 days were included. Then patients with sepsis-associated encephalopathy were screened out by the following exclusion criteria: (1) drug-induced delirium; (2) alcohol-induced delirium; (3) traumatic brain injury; (4) hemorrhagic stroke; (5) cerebral embolism; (6) ischemic stroke; (7) meningitis; (8) encephalitis; (9) epilepsy; (10) metabolic encephalopathy; (11) hypertensive encephalopathy; (12) hepatic encephalopathy; (13) intracranial abscess; (14) other severe liver diseases or kidney diseases affecting consciousness. Sepsis-associated encephalopathy (SAE) was defined as sepsis with a Glasgow Coma Scale (GCS) score of less than 15 on the first day of ICU admission or abnormal neurological findings consistent with delirium[13]. Patients with missing GCS scores were excluded. We employed the minimum GCS score accessible 24 hours after the initiation of ICU admission for each individual.

Variable Extraction

We retrospectively collected the following variables from the MIMIC-IV database: (1) age; (2) sex; (3) ethnicity; (4) vital signs (heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, respiratory rate, and temperature); (5) laboratory results (sodium, potassium, calcium, anion gap, serum creatinine, blood urea nitrogen, chloride, blood glucose, red blood cell,

white blood cell, platelet, hematocrit, red blood cell distribution width, hemoglobin, and international normalized ratio); (6) comorbidities (myocardial infarction, congestive heart failure, anemia, diabetes mellitus, chronic obstructive pulmonary disease, cancer); (7) score system (Charlson Comorbidity Index, Sequential Organ Failure Assessment, Acute Physiology Score III, Glasgow Coma Scale score); (8) treatment (renal replacement therapy, mechanical ventilation, beta-blocker). The exposure factor evaluated in our study was whether they had received dexmedetomidine therapy or not during hospitalization.

Outcomes

The primary outcome was all-cause 28-day mortality, which was defined as all-cause death at 28 days after admission. Secondary outcomes included all-cause in-hospital mortality, ICU and hospital lengths of stay (LOS), and the occurrence of ventilator-associated pneumonia (VAP) during hospitalization. Ventilator-associated pneumonia refers to a hospital-acquired infection that affects individuals receiving mechanical ventilation, characterized by the colonization of bacteria in the upper digestive tract and the subsequent release of contaminated secretions into the lower respiratory tract[14].

Statistical Analysis

Patients were divided into non-dexmedetomidine and dexmedetomidine groups based on whether dexmedetomidine was used or not. The Shapiro-Wilk normality test was conducted on all continuous variables. Continuous variables that met the criteria for normal distribution were represented using the mean and standard deviation (SD), whereas non-normally distributed ones were presented with the median and interquartile range (IQR). Categorical variables were expressed as numerical values and percentages (%). The disparity between the groups was assessed through the utilization of the *t*-test or Wilcoxon rank-sum test for continuous variables and the Chi-square test for categorical variables. Propensity score matching (PSM) analysis was used to minimize confounding factors. To calculate the propensity score for each patient, we used a logistic regression model with covariates listed as follows: age, gender, ethnicity, vital signs, laboratory results, comorbidities, score system, and treatment. For the two groups, a 1:1 nearest propensity score-matching method with a caliper of 0.2 and an inverse probability of treatment weighting (IPTW) were applied to match sepsis-associated encephalopathy patients with similar baseline characteristics. To gauge the efficacy of PSM in mitigating the distinctions between the two cohorts, we calculated the standardized mean difference (SMD), and a lower threshold than 0.1 was treated as acceptable. It is important to highlight that, to prevent the problem of excessive matching, we solely matched variables with SMD>0.1.

Besides, the 28-day survival outcomes after ICU admission for both groups were analyzed with Kaplan-Meier survival curves and compared using the log-rank test. Cox proportional hazard analysis was utilized to explore the association between 28-day mortality, in-hospital mortality, and dexmedetomidine use. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were employed to evaluate this association. Furthermore, subgroup analyses stratified by age, sex, INR, BUN, MI, CHF, cancer, CCI, and MV were performed to assess the robustness of the results. To address potential bias arising from the missing data, variables displaying a missing data percentage surpassing 20% were eliminated from the analysis dataset, whereas the remaining variables were imputed *via* multiple imputation[15]. A p-value<0.05 (two-sided) was considered statistically significant. All statistical analyses were performed using R software (version 4.2.2, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

A total of 4,349 eligible patients with sepsis-associated encephalopathy were identified in this study, and the flowchart of study patients is presented in Figure 1. Between-group comparisons of the baseline characteristics are listed in Table I. Before PSM, the median age of the dexmedetomidine group was 61.53 years old, while that of the non-dexmedetomidine group was 68.25 years old. The dexmedetomidine group had a higher proportion of males (63.3%) compared to the non-dexmedetomidine group (51.9%). On the other hand, the non-dexmedetomidine group had a larger share of white participants. In terms of comorbidities, patients in the dexmedetomidine group were more likely to have myocardial infarction, anemia, and cancer (p<0.05). Additionally, the dexmedetomidine group presented a higher SOFA score, APSIII score, and lower GCS score on admission before PSM (p<0.05). In the following PSM analysis, 1,075 patients who received dexmedetomidine we-

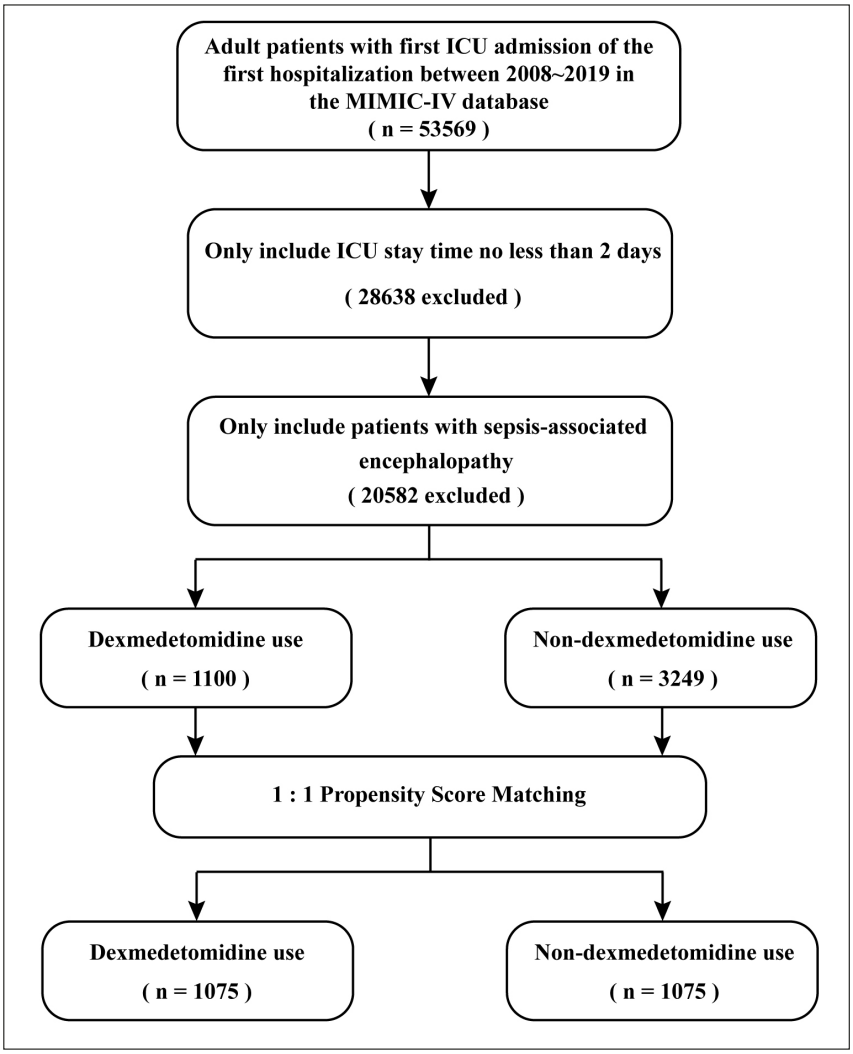

Figure 1. Flow chart of the patient selection in this study.

re matched to 1,075 patients who did not receive dexmedetomidine. After PSM and IPTW, the standardized mean difference (SMD) of all variables was less than 0.1 (Figure 2), and the *p*-values of all variables were greater than 0.05, indicating a satisfactory matching performance.

Relationship between Dexmedetomidine Therapy and Outcomes

Before PSM, the overall 28-day mortality rate of patients with SAE was 14.2% (Table II). Approximately 16.3% and 7.8% 28-day mortality rates occurred in the non-dexmedetomidine and dexmedetomidine groups, respectively ($p<0.001$). The overall in-hospital mortality rate was 11.1%, with 12.4% and 7.2% in the non-dexmedetomidine and dexmedetomidine use groups, respectively ($p<0.001$). Obviously, dexmedetomidine use was associated with a longer stay both in the ICU and hospital ($p<0.001$). The overall VAP incidence was 7.2%, with 5.4% and 12.6% in the non-dexmedetomidine and dexmedetomidine use groups, respectively ($p<0.001$). Similar results were observed in the post-matched cohort compared to the pre-matched cohort. The dexmedetomidine group showed lower 28-day mortality and in-hospital mortality than the non-dexmedetomidine group ($p<0.001$). Additionally, dexmedetomidine therapy is associated with longer stays in both ICU and hospital ($p<0.001$). Moreover, the VAP incidence of the dexmedetomidine group was significantly higher compared to the non-dexmedetomidine group (12.6% *vs.* 8.4%, $p<0.001$), which was almost 50% higher than the other group.

After PSM, individuals without dexmedetomidine therapy during hospitalization had significantly lower 28-day survival than those with dexmedetomidine therapy (log-rank test: $p<0.001$) (Figure 3). HRs of the two groups in the multivariable Cox models before PSM,

Table I. Baseline characteristics of patients in the full cohort and propensity score matched cohort.

Characteristics	Full cohort				Matched cohort			
	Non-DEX group (n=3,249)	DEX group (n=1,100)	SMD	*p*-value	Non-DEX group (n=1,075)	DEX group (n=1,075)	SMD	*p*-value
Age, years†	68.25 [56.48, 79.54]	61.53 [49.43, 73.11]	0.366	<0.001	62.47 [48.93, 73.11]	61.83 [49.90, 73.27]	0.025	0.956
Male§	1686 (51.9)	696 (63.3)	0.232	<0.001	678 (63.1)	675 (62.8)	0.006	0.929
Ethnicity§			0.165	<0.001			0.010	0.974
White	2238 (68.9)	690 (62.7)			681 (63.3)	680 (63.3)		
Black	186 (5.7)	50 (4.5)			52 (4.8)	50 (4.7)		
Others	825 (25.4)	360 (32.7)			342 (31.8)	345 (32.1)		
Weight†	77.03 [65.00, 91.00]	83.00 [69.40, 97.82]	0.232	<0.001	80.45 [68.78, 96.12]	82.85 [69.30, 97.70]	0.011	0.266
Vital signs†								
HR, bpm	87.00 [76.00, 102.00]	88.00 [79.00, 102.00]	0.052	0.085	87.00 [76.00, 102.00]	88.00 [79.00, 102.50]	0.018	0.550
SBP, mmHg	121.00 [106.00, 140.00]	119.00 [106.00, 138.00]	0.012	0.291	120.00 [105.00, 140.00]	119.00 [106.00, 138.00]	0.016	0.843
DBP, mmHg	65.00 [55.00, 77.00]	67.00 [57.00, 79.00]	0.099	0.012	66.00 [56.00, 77.50]	67.00 [57.00, 79.00]	0.059	0.219
MBP, mmHg	82.00 [71.00, 94.00]	83.00 [73.00, 96.00]	0.089	0.015	82.00 [71.00, 94.50]	83.00 [73.00, 96.00]	0.073	0.131
RR, bpm	18.00 [15.00, 22.00]	18.00 [15.00, 22.00]	0.034	0.310	18.00 [15.00, 22.00]	18.00 [15.00, 22.00]	0.004	0.852
T, °C	36.70 [36.30, 37.11]	36.83 [36.44, 37.22]	0.177	<0.001	36.80 [36.39, 37.22]	36.83 [36.44, 37.22]	0.009	0.651
Laboratory tests†								
Na^+, mmol/L	139.00 [136.00, 141.00]	139.00 [137.00, 141.25]	0.075	0.004	139.00 [136.00, 141.00]	139.00 [137.00, 141.00]	0.044	0.224
K^+, mmol/L	4.10 [3.70, 4.50]	4.10 [3.80, 4.50]	0.087	0.019	4.10 [3.70, 4.50]	4.10 [3.70, 4.50]	0.096	0.094
Ca^{2+}, mmol/L	8.30 [7.80, 8.80]	8.30 [7.80, 8.80]	0.009	0.858	8.30 [7.80, 8.70]	8.30 [7.80, 8.80]	0.074	0.116
AG, mmol/L	14.00 [12.00, 16.00]	14.00 [12.00, 16.00]	<0.001	0.632	14.00 [12.00, 16.00]	14.00 [12.00, 16.00]	<0.001	0.727
SCr, mg/dL	0.80 [0.70, 1.10]	0.80 [0.70, 1.00]	0.071	0.550	0.90 [0.70, 1.10]	0.80 [0.70, 1.00]	0.067	0.121
BUN, mg/dL	17.00 [12.00, 24.00]	16.00 [12.00, 21.00]	0.168	<0.001	16.00 [12.00, 22.00]	16.00 [12.00, 21.00]	0.013	0.094
Cl^-, mmol/L	104.00 [100.00, 109.00]	105.00 [101.00, 109.00]	0.064	0.074	105.00 [100.00, 109.00]	105.00 [101.00, 109.00]	0.038	0.516
Glu, mg/dL	131.00 [107.00, 164.00]	127.00 [107.00, 161.25]	0.004	0.359	130.00 [108.00, 161.50]	127.00 [107.00, 161.00]	0.018	0.533
RBC, 10^{12}/L	3.69 [3.09, 4.27]	3.80 [3.20, 4.40]	0.104	0.002	3.76 [3.15, 4.36]	3.79 [3.20, 4.39]	0.001	0.819
WBC, 10^9/L	11.90 [8.30, 16.20]	11.90 [8.80, 16.90]	0.021	0.108	12.30 [8.30, 16.50]	11.90 [8.80, 16.80]	0.006	0.689

(Table continued)

Table I *(Continued)*. Baseline characteristics of patients in the full cohort and propensity score matched cohort.

Characteristics	Full cohort				Matched cohort			
	Non-DEX group (n=3,249)	DEX group (n=1,100)	SMD	*p*-value	Non-DEX group (n=1,075)	DEX group (n=1,075)	SMD	*p*-value
PLT, 10^9/L	204.00 [145.00, 276.00]	203.00 [147.00, 269.00]	0.033	0.418	203.00 [145.00, 268.00]	203.00 [147.00, 270.00]	0.003	0.984
HCT, %	33.70 [28.50, 38.60]	34.75 [29.17, 39.90]	0.122	<0.001	34.50 [28.90, 39.40]	34.70 [29.10, 39.85]	0.005	0.679
RDW, %	14.10 [13.30, 15.50]	13.90 [13.20, 15.10]	0.132	<0.001	13.90 [13.20, 15.30]	13.90 [13.20, 15.10]	0.031	0.543
Hb, g/dL	11.10 [9.40, 12.90]	11.40 [9.50, 13.30]	0.107	0.001	11.30 [9.50, 13.10]	11.40 [9.50, 13.25]	0.011	0.604
INR	1.20 [1.10, 1.50]	1.20 [1.10, 1.40]	0.122	0.004	1.20 [1.10, 1.50]	1.20 [1.10, 1.40]	0.044	0.077
Comorbidities[§]								
MI	482 (14.8)	176 (16.0)	0.032	0.377	159 (14.8)	175 (16.3)	0.041	0.372
CHF	797 (24.5)	242 (22.0)	0.060	0.097	249 (23.2)	235 (21.9)	0.031	0.502
Anemia	1,367 (42.1)	520 (47.3)	0.105	0.003	517 (48.1)	501 (46.6)	0.030	0.517
DM	771 (23.7)	238 (21.6)	0.050	0.167	234 (21.8)	236 (22.0)	0.005	0.958
COPD	864 (26.6)	293 (26.6)	0.001	1.000	274 (25.5)	286 (26.6)	0.025	0.589
Cancer	494 (15.2)	109 (9.9)	0.160	<0.001	108 (10.0)	108 (10.0)	<0.001	1.000
Score system[†]								
CCI	5.00 [4.00, 7.00]	4.00 [3.00, 6.00]	0.293	<0.001	4.00 [3.00, 6.00]	4.00 [3.00, 6.00]	0.002	0.829
SOFA	6.00 [4.00,8.00]	7.00 [5.00,9.00]	0.326	<0.001	7.00 [5.00, 9.00]	7.00 [5.00, 9.00]	0.011	0.821
APSIII	48.00 [35.00, 65.00]	50.00 [37.00, 68.00]	0.076	0.018	52.00 [37.00, 71.00]	50.00 [37.00, 68.00]	0.059	0.204
GCS	13.00 [8.00, 14.00]	11.00 [7.00, 14.00]	0.194	<0.001	11.00 [6.00, 14.00]	11.00 [7.00, 14.00]	0.019	0.856
Treatment[§]								
RRT	148 (4.6)	37 (3.4)	0.061	0.108	51 (4.7)	35 (3.3)	0.076	0.099
MV	1,895 (58.3)	954 (86.7)	0.671	<0.001	925 (86.0)	929 (86.4)	0.011	0.851
Beta blocker	1,951 (60.0)	721 (65.5)	0.114	0.001	698 (64.9)	703 (65.4)	0.010	0.856

[†]Expressed as median [IQR]; [§]Eexpressed as n (%). DEX, dexmedetomidine; SMD, standard mean difference; IQR, interquartile range; SD, standard deviation; HR, heart rate; bpm, beats/breaths per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RR, Respiratory rate; T, body temperature; AG, anion gap; SCr, serum creatinine; BUN, blood urea nitrogen; Glu, glucose (blood); RBC, red blood cell count; WBC, white blood cell count; PLT, platelet; HCT, hematocrit; RDW, red blood cell distribution width; Hb, hemoglobin; INR, international normalized ratio; MI, myocardial infarction; CHF, congestive heart failure; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; APSIII, Acute Physiology Score III; GCS, Glasgow coma scale; RRT, renal replacement therapy; MV, mechanical ventilation.

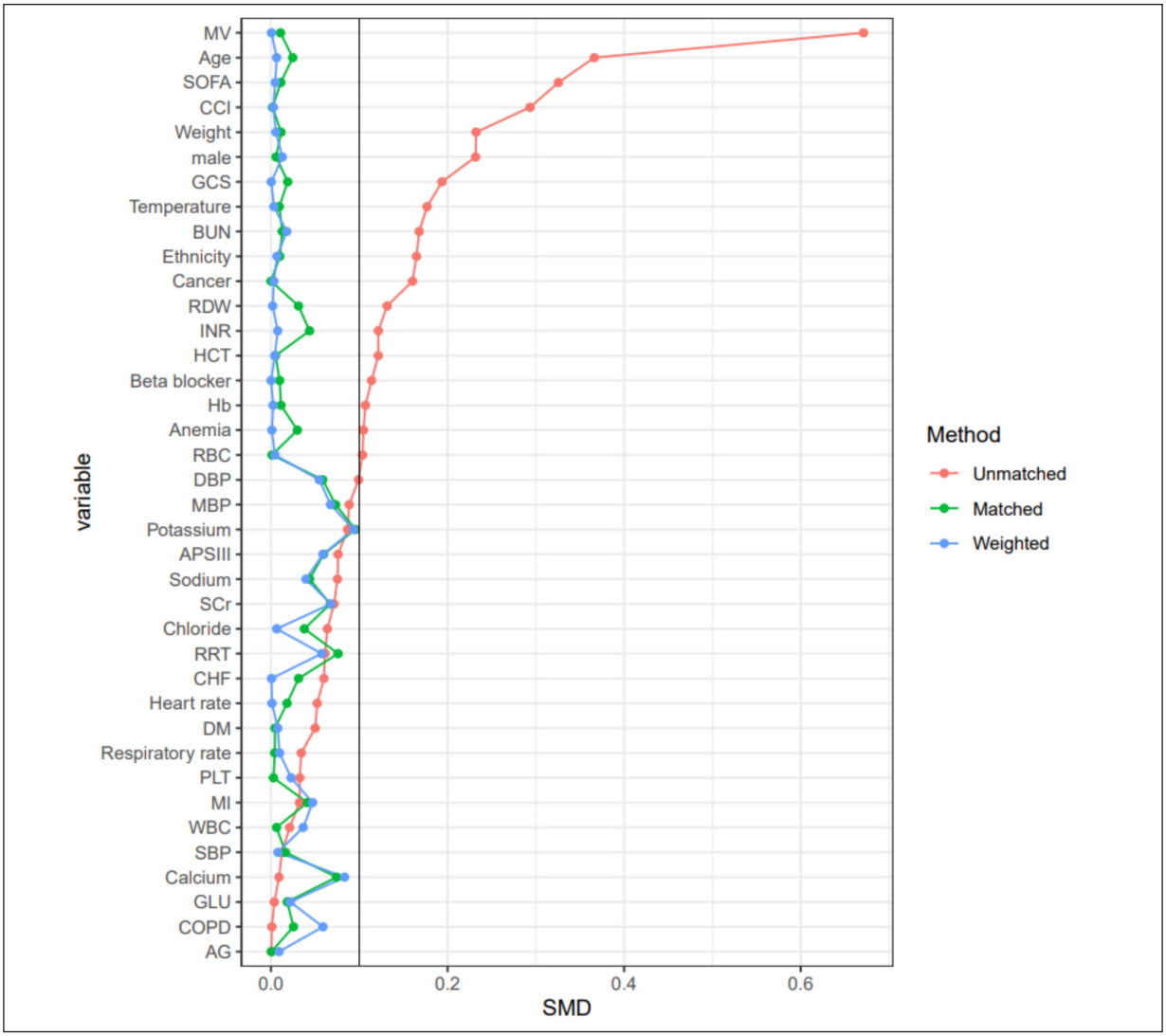

Figure 2. Standardized mean difference of variables before PSM, after PSM and after IPTW.

Table II. Outcomes for the two groups before and after PSM.

Outcomes	Total	Non-DEX group	DEX group	*p*-value
Before PSM				
Patients, n	4,349	3,249	1,100	
28-day mortality, n (%)	617 (14.2)	531 (16.3)	86 (7.8)	<0.001
In-hospital mortality, n (%)	482 (11.1)	403 (12.4)	79 (7.2)	<0.001
Hospital LOS (day), median [IQR]	9.82 [6.36, 15.91]	9.02 [6.06, 14.32]	12.89 [7.96, 20.24]	<0.001
ICU LOS (day), median [IQR]	4.36 [2.95, 7.98]	4.03 [2.84, 6.75]	6.26 [3.68, 11.37]	<0.001
VAP, n (%)	314 (7.2)	175 (5.4)	139 (12.6)	<0.001
After PSM				
Patients, n	2,150	1,075	1,075	
28-day mortality, n (%)	233 (10.8)	148 (13.8)	85 (7.9)	<0.001
In-hospital mortality, n (%)	205 (9.5)	127 (11.8)	78 (7.3)	<0.001
Hospital LOS (day), median [IQR]	11.38 [7.07, 17.81]	10.04 [6.55, 15.93]	12.76 [7.92, 19.95]	<0.001
ICU LOS (day), median [IQR]	5.30 [3.30, 9.79]	4.65 [3.16, 8.55]	6.14 [3.66, 11.04]	<0.001
VAP, n (%)	225 (10.5)	90 (8.4)	135 (12.6)	0.002

PSM, propensity score matching; DEX, dexmedetomidine; IQR, interquartile range; LOS, length of stay; ICU, intensive care unit; VAP, ventilator-associated pneumonia.

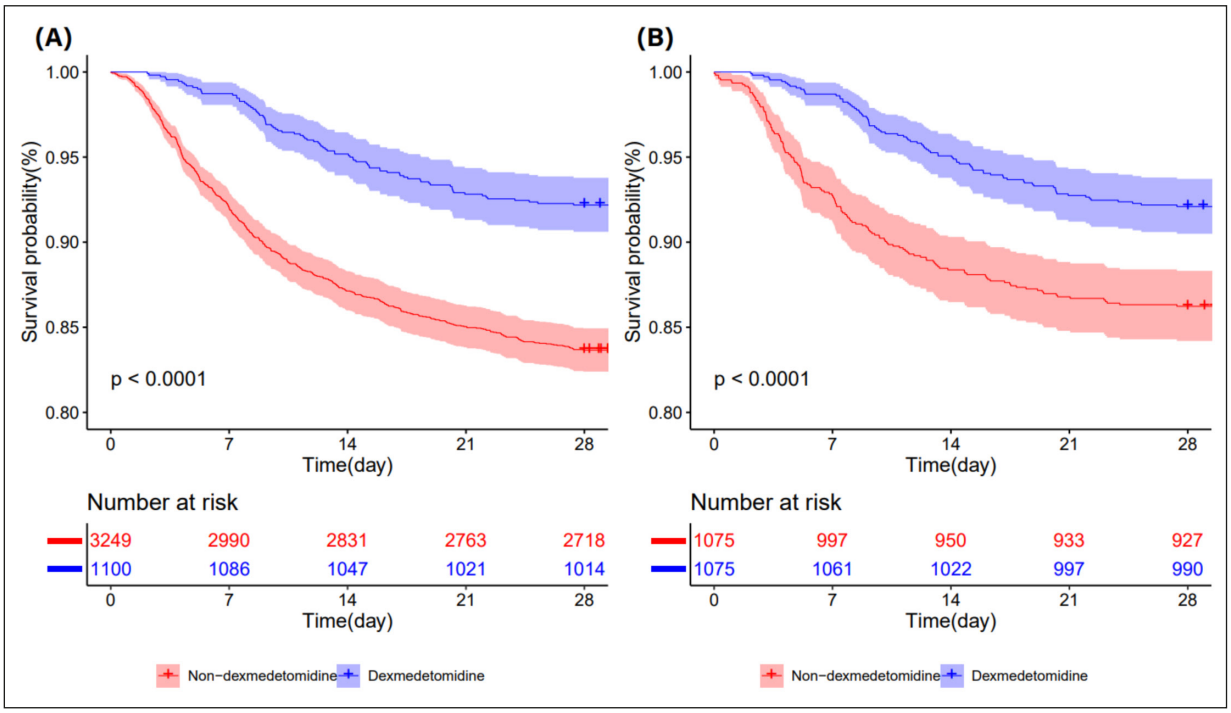

Figure 3. Kaplan-Meier survival curves between the dexmedetomidine and non-dexmedetomidine groups. **A**, Before propensity score matching; (**B**) After propensity score matching.

after PSM and after IPTW were 0.49 (95% CI 0.39-0.62, p<0.001), 0.46 (95% CI 0.35-0.61, p<0.001), and 0.55 (95% CI 0.40-0.75, p<0.001), respectively, demonstrating a significantly beneficial effect of dexmedetomidine use on 28-day mortality of critically ill patients with SAE (Table III). Similarly, HRs of the two groups in the multivariable Cox models before PSM, after PSM and IPTW were 0.53 (95% CI 0.41-0.68, p<0.001), 0.50 (95% CI 0.37-0.67, p<0.001), and 0.63 (95% CI 0.45-0.87, p<0.001), respectively, demonstrating a significant beneficial effect of dexmedetomidine use on in-hospital death of critically ill patients with SAE.

Subgroup Analysis

Although there was an observed association between dexmedetomidine and lower short-term mortality rates in SAE patients, it remained uncertain whether this correlation held true for SAE patients with varying conditions. Hence, a subgroup analysis was conducted. The association between dexmedetomidine treatment and 28-day mortality in different subgroups is depicted in Figure 4. The subgroup analysis revealed consistent effects of dexmedetomidine on 28-day all-cause mortality across most subgroups, including age (<65 and ≥65 years old), sex, INR (<1.2 and ≥1.2), BUN (<16 and ≥16 mg/dL), MI, CHF, cancer, CCI (<4 and

Table III. Association between dexmedetomidine use and outcomes.

Model	HR	95% CI	*p*-value
28-day mortality			
Before PSM	0.49	0.39-0.62	<0.001
After PSM	0.46	0.35-0.61	<0.001
After IPTW	0.55	0.40-0.75	<0.001
In-hospital mortality			
Before PSM	0.53	0.41-0.68	<0.001
After PSM	0.50	0.37-0.67	<0.001
After IPTW	0.63	0.45-0.87	<0.001

The models above were adjusted for the baseline variables shown in Table I. IPTW, inverse probability treatment weighting; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval.

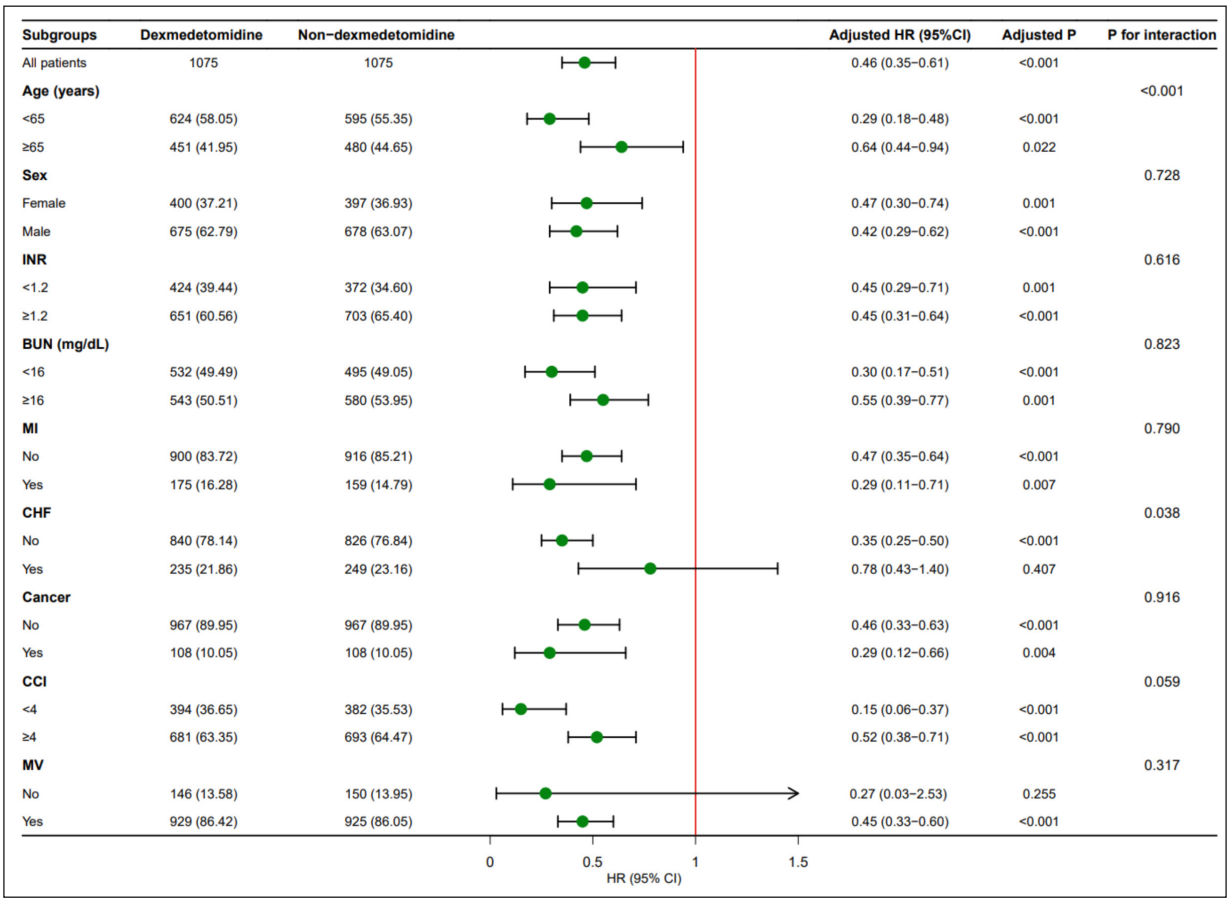

Figure 4. The association between dexmedetomidine therapy and 28-day mortality in different subgroups.

≥4), and mechanical ventilation use. Dexmedetomidine therapy was not significantly associated with favorable outcomes only in patients with CHF (HR 0.78, 95% CI 0.43-1.40, p=0.407) and those without mechanical ventilation use (HR 0.27, 95% CI 0.03-2.53, p=0.255). Moreover, no significant interaction was observed between the dexmedetomidine and non-dexmedetomidine groups in most strata except for the age (p for interaction: <0.001) and CHF (p for interaction: 0.038) groups.

Discussion

This retrospective cohort study evaluated the association of dexmedetomidine administration and short-term outcomes in critically ill patients with sepsis-associated encephalopathy. Our findings indicated that dexmedetomidine treatment was associated with reduced all-cause 28-day and in-hospital mortality rates for SAE patients. Irrespective of whether in the pre-PSM, post-PSM, or post-IPTW cohort, the usage of dexmedetomidine is connected to a reduction in the short-term mortality rate of SAE. After categorizing subgroups by age, sex, INR, BUN, MI, cancer, and CCI, this association remained robust. However, our data also implied that SAE patients who underwent dexmedetomidine therapy encountered increased durations of stay in both the ICU and the hospital. Additionally, the occurrence of ventilator-associated pneumonia (VAP) was higher in patients treated with dexmedetomidine during hospitalization compared to those who did not receive dexmedetomidine therapy.

Sepsis-associated encephalopathy (SAE) has emerged as one of the predominant cerebral disorders among patients in the intensive care unit (ICU). The development of SAE is intricate and influenced by multiple factors, with activated inflammation being acknowledged as a significant contributor. In brief, it is an acute cerebral dysfunction triggered by systemic inflammation caused by sepsis. Systemic inflammation is transmitted to the brain through a compromised blood-brain

barrier (BBB), and the detailed pathophysiological mechanisms comprise leukocytes and microglial activation, lysosomal exocytosis, cytokine release, and free-radical generation[16]. When neurons are subjected to oxidative stress, it induces neuronal dysfunction and cell apoptosis[17]. Nowadays, the modulation of neuroinflammation presents a promising focus for SAE intervention[18]. For instance, studies have shown that INT-777, an agonist of TGR5, can reduce neutrophilic infiltration, and the expression of inflammatory factors in the hippocampus of experimental sepsis rats[19]. Another research[20] revealed that metformin can partially reverse the severe prognosis induced by SAE by suppressing the production of inflammatory factors.

Dexmedetomidine, an α2-adrenergic receptor agonist commonly used for light sedation, has been proven to possess anti-inflammatory properties, thus exerting organ-protective effects. Dexmedetomidine not only serves as a neuroprotectant but also provides protective effects on various organs, including the heart, lungs, liver, kidneys, and intestines, thereby resulting in a lowered overall mortality rate in the murine model[21]. A meta-analysis[22] showed a trend toward improved postoperative outcomes associated with perioperative dexmedetomidine use in surgical patients. Moreover, dexmedetomidine showed potential in reducing pulmonary cell apoptosis and inflammation caused by ischemia-reperfusion injury of the aorta[23]. Clinical trials[24] have reported that dexmedetomidine is effective in reducing acute postoperative delirium compared to a placebo. Recent studies[25] have demonstrated a favorable effect of dexmedetomidine on SAE by rectifying the peripheral shift of Th1/Th2/Th17 and diminishing the production of proinflammatory cytokines in the hippocampus. After receiving dexmedetomidine treatment, inflammatory responses induced by lipopolysaccharide were alleviated in SAE animal models[26]. One potential mechanism contributing to this effect is that dexmedetomidine upregulates the level of netrin-1 to downregulate proinflammatory mediators (e.g., leukotriene-B4) in the central nervous system[27].

After carefully adjusting for confounding factors to the best of our ability, we observed a potential association between the use of dexmedetomidine and prolonged ICU stay and hospital stay. Literature has shown inconsistent outcomes regarding the impact of dexmedetomidine on the length of stay in the ICU and hospital. In a retrospective quality improvement assessment[28] conducted at a tertiary medical center in the United States, a correlation was observed between the utilization of dexmedetomidine and the escalation of ICU and hospital durations. Another single-center cohort study[29] also pointed out that dexmedetomidine expanded the length of ICU stay in critically ill patients. Nevertheless, a few studies[30,31] have suggested that there is no statistically significant correlation between the administration of dexmedetomidine and the duration of ICU or hospitalization. Moreover, some studies[32] supported the reduction of both ICU and hospitalization durations with dexmedetomidine treatment. In our study, the elongation of ICU and hospital stays may be attributed to the decreased mortality rate in the dexmedetomidine group, leading to extended survival time and, consequently, longer hospital treatment.

Notably, our dexmedetomidine cohort exhibited a higher proportion of ventilator-associated pneumonia (VAP) compared to the non-dexmedetomidine group. VAP, a common nosocomial infection in the ICU, occurs in patients mechanically ventilated for more than 48 hours. Despite aggressive efforts to reduce nosocomial infections, the incidence of VAP ranges from 5% to 40%[33]. Certain retrospective observational studies[34] have suggested a possible link between the utilization of sedatives and the development of pneumonia, and furthermore, prospective investigations on sedative discontinuation have reported a potential decrease in the incidence of ventilator-associated pneumonia. Recent research[33] findings have shown that long-lasting hospitalization and impaired consciousness are both risk factors for the occurrence of VAP. Remarkably, our dexmedetomidine cohort exhibited both of these attributes. It is reasonable to suspect that the emergence of this outcome is closely tied to prolonged ICU stays. Extended ICU stays often result in longer duration of intubation, making patients who are on prolonged mechanical ventilation more susceptible to developing VAP. The endotracheal tube (ETT) is recognized as a major factor in the occurrence of VAP. The flow of air moves pathogens towards the lower airways, while decreased tracheal ciliary activity and compromised cough reflex lead to blunted tracheal clearance[35]. Employing strategies such as avoiding intubation, minimizing sedation, and implementing early extubation can effectively enhance outcomes for a few patients[36]. To summarize, the appropriate management of SAE remains a challenge for critical care physicians.

The results of our analysis showed that dexmedetomidine reduced the 28-day mortality among a significant portion of the research populations, regardless of age, gender, physiological and biochemical status, comorbidities, or illness severity, suggesting its potential as a safe and effective treatment. However, our results also suggested that dexmedetomidine did not have a positive effect in patients with CHF. Available studies[37] have previously demonstrated that the dexmedetomidine infusion can prolong the survival time of patients in various subgroups, but it can induce bradycardia and hypotension in critically ill patients with hemodynamic instability, such as those suffering from heart failure. In a retrospective analysis, 17 out of 30 CHF-diagnosed patients manifested symptoms of hypotension following the administration of dexmedetomidine[38]. There was a case report[39] documenting cardiac arrest in two underage individuals after receiving dexmedetomidine infusion, with the potential mechanism being an increase in vagal nerve tension induced by dexmedetomidine. All of the evidence suggests a potential adverse impact of dexmedetomidine on coronary artery and myocardial perfusion, thus necessitating a more cautious approach when considering the use of dexmedetomidine in these populations. In the analysis of age subgroups, it was found that both patients under 65 and those over 65 years of age experienced benefits from dexmedetomidine treatment. However, the *p*-value for interaction was <0.001, suggesting a statistically significant difference in the efficacy of dexmedetomidine treatment across different age categories. In other words, dexmedetomidine treatment yields greater benefits in the younger age group.

Strengths and Limitations

This study was the first to evaluate the effect of dexmedetomidine administration on clinical outcomes in critically ill patients with SAE. However, it is imperative to acknowledge the strengths and limitations of our study. Notably, within the field of dexmedetomidine therapy and SAE, this study stands out for having the largest sample size ever recorded in the existing literature. Apart from that, the propensity score matching (PSM) approach effectively balanced the influence of selection bias. Nevertheless, there are aspects that could be further improved. The influence of dexmedetomidine dosage on short-term outcomes was not considered, and the long-term effects of dexmedetomidine administration on critically ill SAE patients were not observed. The effects of varying dexmedetomidine doses on this population, as well as the long-term implications within this group, merit further exploration. Additionally, this single-center retrospective study calls for multicenter randomized controlled trials to validate these findings. In the future, we need well-designed prospective studies to further confirm our research findings.

Conclusions

This cohort study suggested that dexmedetomidine treatment was associated with decreased 28-day and in-hospital mortality rates of critically ill patients with sepsis-associated encephalopathy. However, our analysis shows that dexmedetomidine administration could not shorten the length of ICU and hospital stay. It could not reduce the incidence of ventilator-associated pneumonia among SAE populations as well. These findings may offer potential guidance when deliberating on the application of dexmedetomidine.

Authors' Contributions

Conceptualization: JT, ZZ. Acquisition of data: JT. Statistical analysis: JT, CW. Methodology: JT, ZZ. All authors have read and approved the final manuscript.

Ethics Approval and Informed Consent

The study was an analysis of a third-party anonymized publicly available database with pre-existing institutional review board (IRB) approval and does not contain protected health information. The authors are qualified to use the data in the MIMIC-IV database. The use of data adhered to ethical guidelines, and no further ethical approvals is needed. Thus, the ethical approval and the need for informed consent were waived for the studies on this database.

Conflicts of Interest

The authors do not have any conflicts of interest in relation to this manuscript.

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Data Availability

Data are available from the corresponding author upon reasonable request.

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