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Delirium as a mediating factor in the survival benefits of dexmedetomidine in acute brain injury management

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Acute brain injury (ABI) is a leading cause of ICU admission and mortality. Effective sedation is essential for preventing secondary brain injury, and dexmedetomidine has emerged as a potential neuroprotective agent. We conducted a retrospective analysis using the MIMIC-IV v3.1 database, including adult patients admitted to the ICU with ABI. Patients were divided into two groups based on whether they received dexmedetomidine. Propensity score matching (PSM), weighting methods, and doubly robust estimation were used to adjust for confounding factors. Results from the doubly robust analysis showed that dexmedetomidine use was significantly associated with reduced in-hospital mortality (HR: 0.41, 95% CI: 0.35–0.48, $p < 0.001$) and ICU mortality (HR: 0.34, 95% CI: 0.28–0.41, $p < 0.001$). Additionally, dexmedetomidine was associated with significantly increased vasopressor-free days (MD: 2.64, 95% CI: 1.98–3.30, $p < 0.001$) and ventilation-free days (MD: 2.23, 95% CI: 1.59–2.86, $p < 0.001$). Further mediation analysis indicated that delirium mediated 37% of the effect of dexmedetomidine on in-hospital mortality and 60% of its effect on ICU mortality. This suggests that delirium may be a key mediator of dexmedetomidine's beneficial effects, consistent with its potential advantages in sedation and neuroprotection observed in previous studies. In conclusion, dexmedetomidine use in ICU patients with ABI is associated with significantly lower mortality and improved clinical outcomes, with delirium acting as a critical mediator.

Keywords Dexmedetomidine, Acute brain injury, Delirium, ICU, Mortality.

Acute brain injury (ABI), including traumatic brain injury (TBI), ischemic stroke, and hemorrhagic stroke, is a leading cause of global morbidity and mortality[1–3]. In 2019, stroke alone accounted for 98.8 million disability-adjusted life-years, while TBI affected an estimated 69 million people annually, with a particularly high burden in low- and middle-income countries[4,5]. ABI typically involves primary brain injury resulting from initial neurological insults and secondary injury processes such as intracranial hypertension and cerebral hypoperfusion. Secondary injury often exacerbates the primary damage, leading to further complications that require intensive care unit (ICU) admission for critical management. In the ICU, effective sedation is essential for managing agitation, controlling intracranial pressure, and reducing physiological stress—factors crucial for survival and neurological recovery[3].

Delirium, a common and serious complication in ICU patients with ABI, is linked to poor outcomes such as higher mortality, longer ICU stays, and lasting cognitive deficits[6,7]. It can worsen secondary brain injury, further hindering recovery. Recent studies suggest that delirium mediates the relationship between sedative use and clinical outcomes in neurocritical care, emphasizing its pivotal role in prognosis. Dexmedetomidine, a selective α2-adrenergic receptor agonist, offers several advantages over conventional sedatives[8]. It reduces the prevalence and severity of delirium, provides neuroprotective effects, and avoids significant respiratory depression, making it an attractive option for neurocritical care[8]. Additionally, its anti-inflammatory, antioxidative, and anti-

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apoptotic properties may offer therapeutic benefits over traditional sedatives, such as propofol and midazolam, particularly in patients at risk of delirium and secondary brain injury.

Despite growing evidence supporting dexmedetomidine's benefits in neurocritical care, its use in ABI patients remains inadequately explored, especially regarding the clinical implications of delirium mediation. Clarifying delirium's role could directly influence sedation strategies by highlighting the importance of delirium prevention, enabling clinicians to tailor ICU sedation protocols specifically to minimize secondary brain injury and improve neurological outcomes. However, previous research has largely overlooked this crucial interaction between delirium and dexmedetomidine, particularly in diverse ABI populations. This study aims to evaluate the relationship between dexmedetomidine use and key clinical outcomes, including mortality and ICU-related measures, while explicitly quantifying delirium's mediating role in these associations.

Methods

Database source

This study utilized data from the Medical Information Mart for Intensive Care (MIMIC-IV v3.1), a publicly available clinical database containing detailed records of ICU admissions at Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2008 to 2022. The MIMIC-IV database includes comprehensive information on patient demographics, clinical characteristics, treatments, and outcomes, making it an invaluable resource for critical care research. The use of this de-identified public database was exempt from institutional review board (IRB) approval, as the data has been anonymized to protect patient privacy. The authorized researcher, Wang Juan, holds record ID:62674475 for accessing MIMIC-IV. All analyses were conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure transparency and reproducibility.

Data collection

Study population

This study included adults aged 18 years or older who experienced their first ICU admission recorded in the MIMIC-IV v3.1 database and were diagnosed specifically with ABI comprising traumatic brain injury (TBI), non-traumatic intracerebral hemorrhage (NICH), or non-traumatic cerebral ischemic stroke (NCIS) based on ICD-9 and ICD-10 codes. Patients who received dexmedetomidine during their ICU stay were classified into the dexmedetomidine group, while those who did not receive this treatment were assigned to the no dexmedetomidine group. Exclusion criteria included non-first ICU admissions, ICU stays shorter than 24 h, and patients younger than 18 years of age.

Delirium was assessed using the Confusion Assessment Method for the ICU (CAM-ICU), a validated tool for diagnosing delirium in critically ill patients[9,10]. According to previous studies, delirium was diagnosed if patients exhibited acute onset or fluctuating mental status changes, inattention, and either disorganized thinking or an altered level of consciousness. Patients meeting these criteria were classified as delirious (CAM-ICU positive).

Data extraction

Data were extracted using Structured Query Language (SQL) queries, with scripts obtained from the MIMIC-IV GitHub repository (https://github.com/MIT-LCP/mimic-iv). Patient characteristics, including sex, age, weight, and comorbidities such as chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CBD), liver disease, renal disease, cancer, diabetes, hypertension, delirium, acute kidney injury (AKI), and sepsis, were collected. ABI etiology was classified into TBI, NICH, and NCIS. Laboratory variables, including hemoglobin (Hb), red blood cell count (RBC), platelet count (PLT), white blood cell count (WBC), blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), glucose, and oxygen saturation (SpO_2), were also extracted. Vital signs, including heart rate (HR), mean blood pressure (MBP), respiratory rate (RR), were recorded within the first 24 h of ICU admission. Organ dysfunction and severity were evaluated using the Charlson Comorbidity Index (CCI), Acute Physiology Score III (APS III), Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA), and GCS scores. ICU interventions, including craniotomy, percutaneous transcatheter cerebral artery intervention (PTCAI), mannitol, midazolam use, propofol use, ketamine and dexmedetomidine administration during the ICU stay and on the first day of ICU admission, as well as the use of mechanical ventilation and vasopressor agents during the first 24 h of ICU admission, were recorded.

Outcome measures

This study's primary outcomes were in-hospital and ICU mortality. Secondary outcomes included mechanical ventilation-free and vasopressor-free days within 28 days of ICU admission.

Statistical analyses

Statistical analyses were performed using R Statistical Software (version 4.2.2) and the Free Statistics analysis platform (version 2.0, Beijing, China). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean ± standard deviation (SD), while non-normally distributed variables were reported as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. Group comparisons were performed using the independent samples t-test or Mann-Whitney U-test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Bonferroni adjustments were applied where necessary to account for multiple comparisons, with statistical significance set at a two-sided p-value < 0.05. To evaluate associations between dexmedetomidine use and primary outcomes, Cox proportional hazards regression models were utilized, with results presented as hazard ratios (HR) and 95% confidence intervals (CI). Kaplan-Meier survival curves were generated, and differences were assessed using the log-rank test. Landmark analyses were performed in the propensity-score-

matched cohort, with survival analyzed from day 3 onward. In addition, a sensitivity analysis was conducted by excluding all patients who experienced the outcome before day 3 prior to matching, with subsequent analyses restricted to those surviving beyond the landmark. Secondary outcomes, being continuous variables, were analyzed using linear regression models, with results reported as mean differences (MD) and corresponding 95% CI. We constructed three sequential Cox regression models assessing associations between dexmedetomidine exposure and mortality outcomes. **Model 1** was unadjusted. **Model 2** was adjusted for demographics, vital signs, and laboratory parameters based on clinical relevance and prior literature (sex, age, weight, heart rate, mean blood pressure, respiratory rate, SpO_2, glucose, hemoglobin, RBC, platelets, WBC, BUN, creatinine, sodium, potassium). **Model 3** additionally adjusted for AKI, sepsis, sedative use (midazolam, propofol, ketamine), and ABI etiology. The total dexmedetomidine duration variable was scaled per 100 h (duration multiplied by 0.01) to facilitate interpretation of effect estimates.

Propensity score (PS) models were applied to balance the treatment groups, dexmedetomidine versus no dexmedetomidine, based on a comprehensive set of baseline covariates[11]. These included demographic factors (age, sex, weight), clinical variables (HR, MBP, RR, SpO_2, glucose, Hb, renal function markers such as BUN and creatinine), comorbid conditions (COPD, CBD, liver disease, renal disease, cancer, diabetes, hypertension), and clinical severity scores (CCI, APS III, SAPS II, GCS, SOFA). Surgical interventions and ICU treatments, including craniotomy, mechanical ventilation, and vasopressor use during the first 24 h of ICU admission, were also considered. The effectiveness of the propensity score model was evaluated using the Receiver Operating Characteristic (ROC) curve, with the area under the curve (AUC) reported to demonstrate the model's discriminative ability. Standardized mean differences (SMDs) were calculated to assess covariate balance after matching, with smaller SMD values indicating improved balance. In addition to propensity score matching (PSM) and propensity score adjustment (PSA), various weighting methods were employed, including Inverse Probability of Treatment Weighting (IPTW), Standardized Mortality Ratio Weighting (SMRW), pairwise algorithmic (PA) weighting, and Overlap Weighting (OW). SMDs were used to assess covariate balance across these methods[12]. Furthermore, a doubly robust approach was applied, combining both propensity score adjustment and multivariable regression, to ensure more accurate estimation of treatment effects. These weighting methods were selected due to their complementary advantages: IPTW effectively reduces confounding by weighting according to the inverse probability of treatment; SMRW specifically adjusts for baseline covariate differences to standardize comparisons across groups; PA weighting allows for clear and direct comparisons between treatment pairs; and OW highlights the subgroup of patients with clinical equipoise, improving result generalizability. Mediation analysis was conducted using a doubly robust estimation method with bootstrap sampling (1000 iterations) to evaluate the mediating role of delirium in the relationship between dexmedetomidine use and mortality outcomes.

Subgroup analyses within the matched cohort were performed to identify potential effect modifiers. Subgroups included age (< 65 vs. ≥65 years), sex (female vs. male), presence of hypertension, diabetes, and craniotomy. Interaction terms were used to evaluate group heterogeneity. Missing data were imputed using multiple imputation by chained equations (MICE). Sensitivity analyses were performed to assess the robustness of results under various conditions. The frequency and percentage of missing data for each covariate are summarized in Supplementary Table 11 Additional sensitivity analyses were performed: (1) excluding patients with missing covariate data; (2) employing multiple propensity score (PS) methods (PSM, IPTW, SMRW, PA, OW) to test consistency; (3) examining robustness specifically in the subgroup of ICU patients receiving dexmedetomidine on the first ICU day using these PS methods and corresponding mediation analyses; (4) conducting additional propensity score matching and mediation analyses adjusted for clinically relevant variables (AKI, sepsis, midazolam use, propofol use, ketamine use, and ABI etiology).

Results

Cohort characteristics

The cohort included 7,490 patients with ABI who were admitted to the ICU for the first time, of whom 1,143 received dexmedetomidine and 6,347 did not. After PSM, 1,128 patients remained in each group (Supplementary Fig. S1). In the matched cohort, baseline characteristics were well balanced between the dexmedetomidine and no dexmedetomidine groups. In the dexmedetomidine group, 65.6% were male, compared to 65.0% in the no dexmedetomidine group. Common comorbidities in the no dexmedetomidine group included CBD (68.7%), hypertension (65.9%), and diabetes (25.6%). The rates of craniotomy were 25.5% in the dexmedetomidine group and 26.6% in the no dexmedetomidine group, while the rates of PTCAI were 13.2% and 12.5%, respectively (Table 1). Similarly, baseline characteristics remained well balanced between groups in the 3-day landmark sensitivity analysis cohort (Supplementary Table S2).

The ROC curve for the propensity score model (AUC = 81.1%) and the substantial reduction in SMDs after matching and weighting are shown in Supplementary Fig. S2 which demonstrates improved balance between the dexmedetomidine and matched control groups across different matching and weighting methods, including IPTW, SMRW, PA, and OW.

Dexmedetomidine use during ICU stay and within the first 24 h of ICU admission was associated with reduced mortality, as shown in Supplementary Table 3. This association, along with age, comorbidities, and interventions, was linked to both in-hospital and ICU mortality in ABI patients. Hazard ratios (HR) before and after interpolation remained consistent.

Clinical outcomes

Dexmedetomidine use was consistently associated with reduced in-hospital and ICU mortality across all analytical methods. For in-hospital mortality, HRs ranged from 0.37 (95% CI: 0.31–0.45, $p < 0.001$) in the PSM analysis to 0.55 (95% CI: 0.47–0.65, $p < 0.001$) in the unmatched crude analysis. Similarly, for ICU mortality, HRs

	Original cohort			Matched cohort		
Covariate	**No dexmedetomidine**	**Dexmedetomidine**	**SMD**	**No dexmedetomidine**	**Dexmedetomidine**	**SMD**
	***n* = 6347**	***n* = 1143**		***n* = 1128**	***n* = 1128**	
Sex, Male, n (%)	3351 (52.8)	750 (65.6)	0.263	733 (65)	740 (65.6)	0.013
Age, years	68.0 ± 17.1	60.3 ± 17.6	0.445	60.6 ± 18.6	60.6 ± 17.4	0.003
Weight, kg	78.0 ± 24.4	82.3 ± 22.7	0.184	80.6 ± 21.1	82.3 ± 22.7	0.075
Heart Rate, bpm	79.9 ± 14.5	83.5 ± 15.1	0.247	84.5 ± 15.7	83.4 ± 15.0	0.073
MBP, mmHg	85.0 ± 11.1	83.1 ± 10.4	0.17	83.3 ± 10.4	83.2 ± 10.4	0.005
Respiratory Rate, bpm	18.5 ± 3.2	19.3 ± 3.6	0.232	19.3 ± 3.8	19.3 ± 3.5	0.016
SpO_2, %	97.0 ± 1.9	97.9 ± 1.8	0.444	98.0 ± 1.7	97.9 ± 1.8	0.079
Glucose, mg/dL	158.5 ± 1793.3	141.1 ± 44.3	0.014	141.2 ± 42.3	141.0 ± 44.3	0.005
Hemoglobin, g/dL	11.5 ± 2.2	10.9 ± 2.3	0.273	10.8 ± 2.5	10.9 ± 2.3	0.031
RBC, ×10^6/μL	3.7 ± 1.1	3.6 ± 0.9	0.081	3.6 ± 1.0	3.6 ± 0.9	0.029
PLT, ×10^9/L	201.8 ± 81.8	184.7 ± 84.5	0.206	185.3 ± 86.4	185.1 ± 84.2	0.003
WBC, ×10^9/L	12.5 ± 9.6	14.9 ± 7.1	0.277	14.8 ± 11.6	14.7 ± 6.6	0.004
BUN, mg/dL	17.0 (13.0, 24.0)	18.0 (13.0, 25.0)	0.088	17.0 (13.0, 25.0)	18.0 (13.0, 25.0)	0.028
Creatinine, mg/dL	0.9 (0.8, 1.2)	1.0 (0.8, 1.3)	0.136	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	0.025
Sodium, mEq/L	140.8 ± 4.9	141.5 ± 4.9	0.128	141.4 ± 5.5	141.5 ± 4.9	0.01
Potassium, mEq/L	3.8 ± 0.5	3.8 ± 0.5	0.081	3.8 ± 0.5	3.8 ± 0.5	0.015
COPD, n (%)	888 (14)	162 (14.2)	0.005	172 (15.2)	162 (14.4)	0.025
CBD, n (%)	4805 (75.7)	800 (70)	0.129	775 (68.7)	790 (70)	0.029
Liver Disease, n (%)	317 (5)	91 (8)	0.121	96 (8.5)	89 (7.9)	0.023
Renal Disease, n (%)	795 (12.5)	153 (13.4)	0.026	157 (13.9)	150 (13.3)	0.018
Cancer, n (%)	531 (8.4)	71 (6.2)	0.083	70 (6.2)	69 (6.1)	0.004
Diabetes, n (%)	1498 (23.6)	287 (25.1)	0.035	289 (25.6)	285 (25.3)	0.008
Hypertension, n (%)	4360 (68.7)	776 (67.9)	0.017	743 (65.9)	768 (68.1)	0.047
CCI	5.3 ± 3.0	4.6 ± 3.1	0.228	4.6 ± 3.2	4.6 ± 3.1	0.014
APS III	37.7 ± 17.7	42.1 ± 19.1	0.235	42.7 ± 22.0	41.9 ± 18.8	0.036
SAPS II	33.3 ± 12.4	35.5 ± 12.9	0.174	36.0 ± 14.0	35.4 ± 12.8	0.047
GCS	14.1 ± 2.0	14.4 ± 1.8	0.146	14.3 ± 2.1	14.3 ± 1.8	0.016
SOFA	4.2 ± 3.0	6.7 ± 3.4	0.786	6.6 ± 3.9	6.6 ± 3.3	0.005
Craniotomy, n (%)	1186 (18.7)	289 (25.3)	0.16	300 (26.6)	288 (25.5)	0.024
PTCAI, n (%)	929 (14.6)	149 (13)	0.046	141 (12.5)	149 (13.2)	0.021
Mannitol, n (%)	548 (8.6)	147 (12.9)	0.137	155 (13.7)	145 (12.9)	0.026
Ventilation day 1, n (%)	1435 (22.6)	681 (59.6)	0.811	681 (60.4)	667 (59.1)	0.025
Vasopressor day 1, n (%)	791 (12.5)	256 (22.4)	0.264	276 (24.5)	251 (22.3)	0.052

Table 1. Baseline characteristics of selected patients with acute brain injury (ABI). Continuous variables with normal distribution are expressed as mean ± SD; variables with non-normal distribution (BUN and creatinine) as median [IQR]; categorical variables as n (%). Abbreviations: ABI, acute brain injury; APS III, Acute Physiology Score III; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CBD, cerebrovascular disease; MBP, mean blood pressure; SD, standard deviation; SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment; PTCAI, percutaneous transcatheter cerebral artery intervention.

ranged from 0.30 (95% CI: 0.25–0.38, $p < 0.001$) in the PSM analysis to 0.42 (95% CI: 0.35–0.51, $p < 0.001$) in the unmatched crude analysis. These findings remained consistent across various analytical methods, including multivariable adjustment, propensity score adjustment, and weighting approaches (IPTW, SMRW, PA, OW). The doubly robust analysis also demonstrated consistent protective effects, with HRs for in-hospital mortality and ICU mortality of 0.41 (95% CI: 0.35–0.48, $p < 0.001$) and 0.34 (95% CI: 0.28–0.41, $p < 0.001$), respectively.

For secondary outcomes, dexmedetomidine use was associated with significantly increased vasopressor-free and ventilation-free days. In the PSM analysis, MDs were 3.18 days (95% CI: 2.19–4.17, $p < 0.001$) for vasopressor-free days and 2.79 days (95% CI: 1.83–3.75, $p < 0.001$) for ventilation-free days. These results were consistent across other methods, including doubly robust estimation, with MDs for vasopressor-free and ventilation-free days of 2.64 days (95% CI: 1.98–3.30, $p < 0.001$) and 2.23 days (95% CI: 1.59–2.86, $p < 0.001$), respectively. While the effect on ventilation-free days was not statistically significant in the Weighted IPTW analysis (MD: 0.30, 95% CI: −0.46 to 1.07, $p = 0.442$), the point estimate suggests a trend toward increased ventilation-free days. Sensitivity analyses presented in Supplementary Tables 4 and 5, excluding missing covariate data and using data from the first day of ICU admission when dexmedetomidine was administered, respectively, yielded results consistent with those in Table 3. Additional sensitivity analyses incorporating further clinically relevant variables

Method	In-Hospital Mortality		ICU Mortality		Vasopressor-Free in 28 Days		Ventilation-Free in 28 Days	
	HR (95% CI)	*P*	HR (95% CI)	*P*	MD (95% CI)	*P*	MD (95% CI)	*P*
Unadjusted (Crude)	0.55 (0.47 ~ 0.65)	< 0.001	0.42 (0.35 ~ 0.51)	< 0.001	−0.63 (−1.34 ~ 0.07)	0.08	−1.74 (−2.44~−1.03)	< 0.001
Multivariable Adjusted	0.41 (0.35 ~ 0.48)	< 0.001	0.34 (0.28 ~ 0.41)	< 0.001	2.67 (2.02 ~ 3.33)	< 0.001	2.24 (1.6 ~ 2.88)	< 0.001
PSA	0.4 (0.34 ~ 0.48)	< 0.001	0.33 (0.27 ~ 0.4)	< 0.001	2.39 (1.63 ~ 3.15)	< 0.001	1.95 (1.2 ~ 2.69)	< 0.001
PSM	0.37 (0.31 ~ 0.45)	< 0.001	0.3 (0.25 ~ 0.38)	< 0.001	3.18 (2.19 ~ 4.17)	< 0.001	2.79 (1.83 ~ 3.75)	< 0.001
IPTW	0.49 (0.41 ~ 0.58)	< 0.001	0.36 (0.29 ~ 0.44)	< 0.001	0.75 (−0.02 ~ 1.52)	0.056	0.3 (−0.46 ~ 1.07)	0.442
SMRW	0.34 (0.3 ~ 0.4)	< 0.001	0.28 (0.23 ~ 0.33)	< 0.001	4.03 (3.2 ~ 4.86)	< 0.001	3.6 (2.8 ~ 4.41)	< 0.001
PA	0.38 (0.31 ~ 0.46)	< 0.001	0.29 (0.23 ~ 0.36)	< 0.001	3.05 (2.51 ~ 3.6)	< 0.001	2.7 (2.18 ~ 3.23)	< 0.001
OW	0.39 (0.31 ~ 0.49)	< 0.001	0.3 (0.23 ~ 0.39)	< 0.001	2.61 (2.07 ~ 3.14)	< 0.001	2.21 (1.69 ~ 2.74)	< 0.001
Doubly Robust	0.41 (0.35 ~ 0.48)	< 0.001	0.34 (0.28 ~ 0.41)	< 0.001	2.64 (1.98 ~ 3.3)	< 0.001	2.23 (1.59 ~ 2.86)	< 0.001

Table 2. Primary and secondary outcome analysis for Dexmedetomidine use on mortality and ICU outcomes. Analyses evaluated the association between dexmedetomidine use during ICU stay and primary outcomes (in-hospital and ICU mortality, reported as HR) and secondary outcomes (28-day vasopressor- and ventilation-free days, reported as MD). Methods included crude analysis, multivariable adjustment, propensity score–based approaches (adjustment, matching, and weighting: IPTW, SMRW, PA, OW), and doubly robust estimation. HR, hazard ratio; MD, mean difference; IPTW, inverse probability of treatment weighting; SMRW, standardized mortality ratio weighting; PA, pairwise algorithmic; OW, overlap weighting.

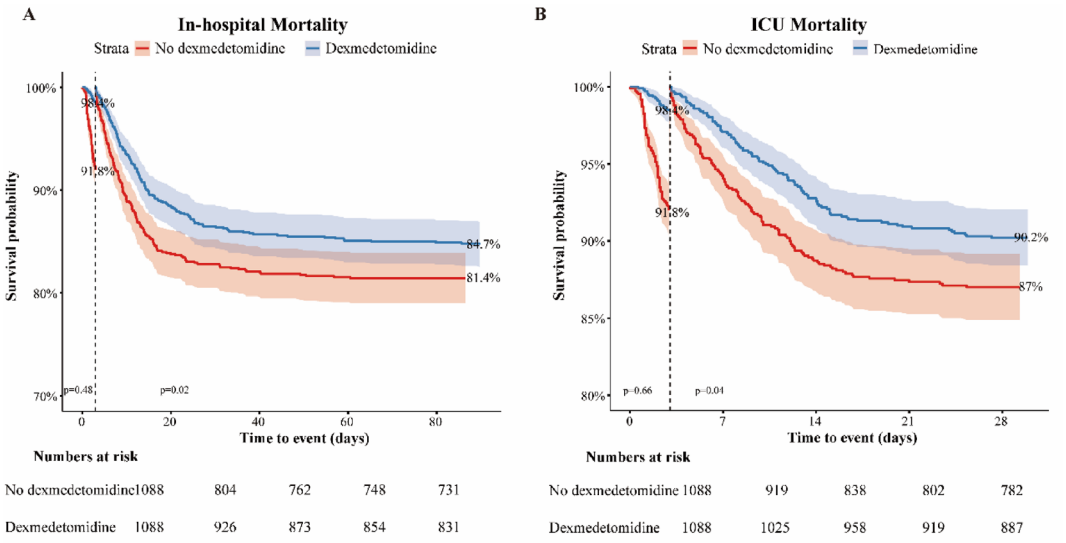

Fig. 1. Landmark Analysis of Dexmedetomidine Use and Mortality Outcomes. Landmark Kaplan-Meier survival curves starting from day 3 post-ICU admission for (A) in-hospital mortality and (B) ICU mortality, stratified by dexmedetomidine use. Survival probabilities (with 95% CI represented by shaded areas), numbers at risk at specified time intervals, and corresponding p-values are displayed. The landmark time (day 3) was selected based on previous literature.

(ABI etiology, AKI, sepsis, midazolam use, propofol use, and ketamine use) also confirmed the robustness of our primary and secondary outcomes (Supplementary Table 6). Furthermore, results remained consistent in the 3-day landmark cohort (Supplementary Table S7).

Additional analyses showed that higher total dexmedetomidine dose and longer duration of use were significantly associated with reduced risks of both in-hospital and ICU mortality, consistently observed across progressively adjusted models (Supplementary Table 8).

In the matched cohort, landmark analyses starting from day 3 after ICU admission (Fig. 1) showed significantly improved survival among patients receiving dexmedetomidine compared to those not receiving dexmedetomidine, for both in-hospital mortality ($p = 0.02$) and ICU mortality ($p = 0.04$). Kaplan–Meier survival analyses are shown in Supplementary Fig. S3 (propensity-score-matched cohort) and Supplementary Fig. S4 (matching performed after exclusion of patients with events before the 3-day landmark).

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Subgroup analysis

Subgroup analyses (Fig. 2) demonstrated that dexmedetomidine use was consistently associated with reduced in-hospital and ICU mortality across all examined subgroups. HRs indicated a protective effect, irrespective of age, sex, comorbidities, or intervention status. Additional subgroup analyses by acute brain injury etiology (Supplementary Fig. S5 and Supplementary Table 9) showed similar trends, with no significant interaction for in-hospital mortality (interaction $p = 0.085$) or ICU mortality (interaction $p = 0.162$), suggesting consistent benefits of dexmedetomidine across ABI subtypes.

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Mediation analysis: the role of delirium

In the matched cohort, mediation analyses assessed the role of delirium in the associations between dexmedetomidine use and clinical outcomes.

For in-hospital mortality, delirium mediated 37% of the total effect of dexmedetomidine (total effect estimate: −0.114, 95% CI: −0.149 to −0.076). The direct effect of dexmedetomidine on in-hospital mortality was − 0.072 (95% CI: −0.108 to −0.030), while the indirect effect mediated through delirium was − 0.042 (95% CI: −0.065 to −0.023) (Fig. 3A). Similarly, for ICU mortality, delirium mediated 60% of the total effect (total effect estimate: −0.107, 95% CI: −0.147 to −0.071). The direct effect was − 0.043 (95% CI: −0.084 to 0.001), and the indirect effect via delirium was − 0.064 (95% CI: −0.091 to −0.041) (Fig. 3B). For secondary outcomes, delirium mediated 42% of the effect on vasopressor-free days and 33% on ventilation-free days within 28 days (Figs. 3C–D). Detailed values can be found in Supplementary Table 10.

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Sensitivity analyses based on ICU patients who received dexmedetomidine on Day 1 (Supplementary Table 11, Supplementary Fig. 6), together with additional mediation analyses adjusted for clinically relevant covariates (Supplementary Table 12) and mediation results from the 3-day landmark sensitivity analysis cohort (Supplementary Fig. S7), all confirmed the robustness of these findings.

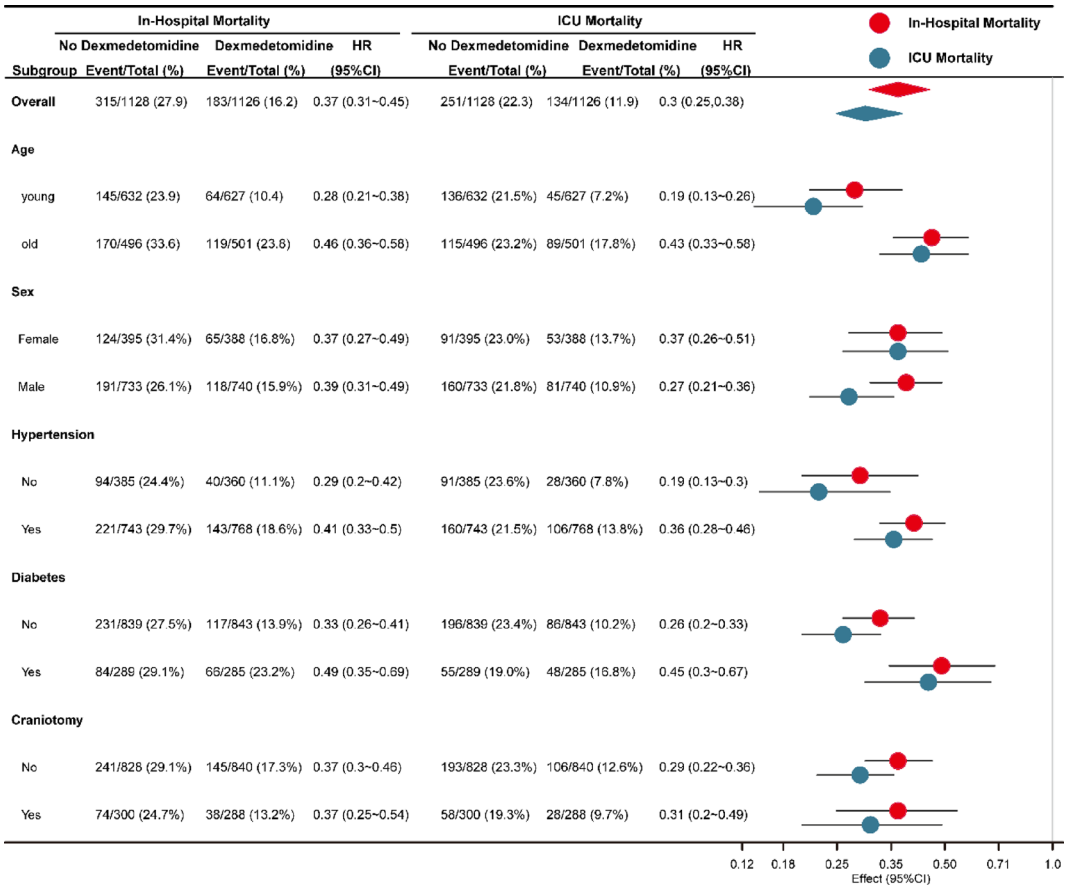

Fig. 2. Subgroup analysis of in-hospital and ICU mortality.Forest plots displaying HR and 95%CIsfor in-hospital mortality (red) and ICU mortality (blue) in subgroups from the matched cohort. Analyses included subgroups defined by age, sex, hypertension, diabetes, and craniotomy status.

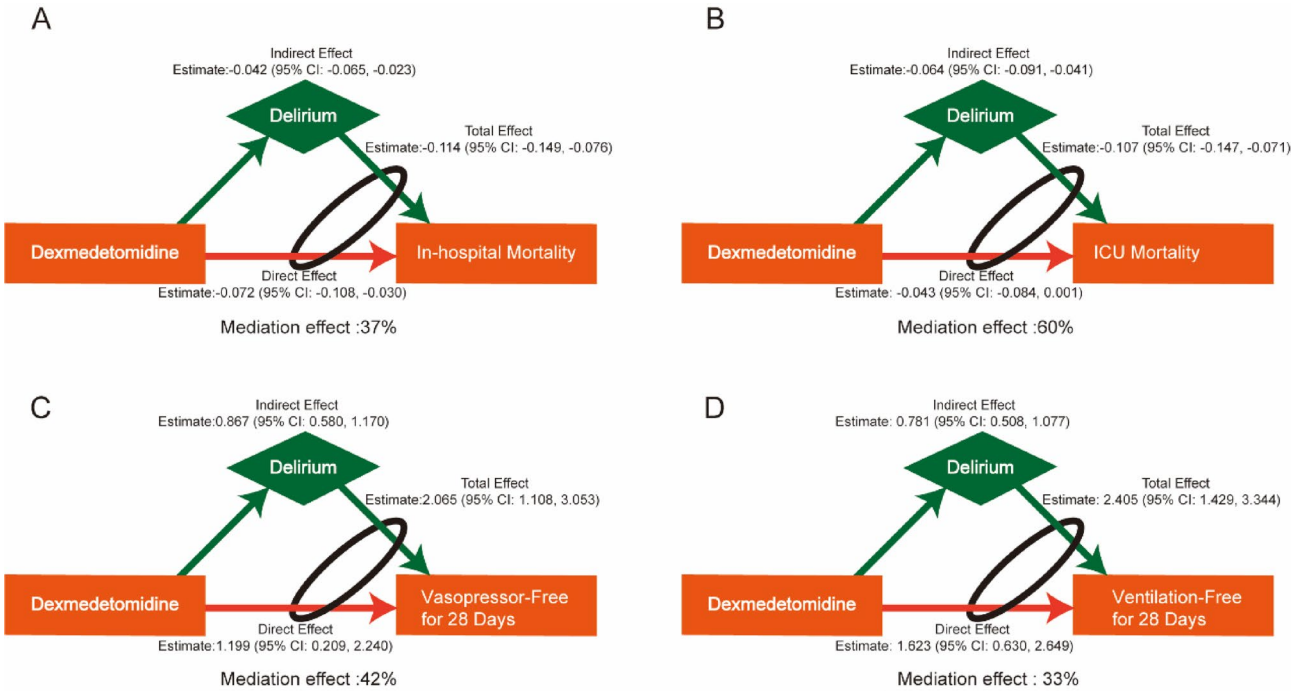

Fig. 3. Mediation Analysis of the Effect of Dexmedetomidine on Clinical Outcomes in ABI Through Delirium.Panel A shows a significant reduction in in-hospital mortality, with delirium mediating 37% of the effect. Panel B demonstrates a substantial reduction in ICU mortality, with delirium accounting for a 60% mediation effect. Panel C reveals a moderate 42% mediation effect on 28-day vasopressor-free probability, and Panel D indicates a 32% mediation effect on 28-day ventilation-free probability.

Discussion

This study demonstrates that the use of dexmedetomidine in ICU patients with brain injuries is consistently associated with marked reductions in both in-hospital and ICU mortality. Additionally, it is linked to improvements in secondary outcomes, including increased vasopressor-free and ventilation-free days within the first 28 days of admission. These findings remained robust across multiple analytical methods, including PSM, PSA and various weighting approaches (IPTW, SMRW, PA, OW). Mediation analysis revealed that delirium significantly mediated dexmedetomidine's protective effects, contributing to 37% of the reduction in in-hospital mortality, 60% in ICU mortality, and 42% and 33% of the improvements in vasopressor-free and ventilation-free days. These results underscore the pivotal role of delirium management in enhancing survival and recovery among ICU patients treated with dexmedetomidine.

Dexmedetomidine's anti-inflammatory and sedative properties significantly improve outcomes in critically ill patients[8,13], expanding from sedation in mechanically ventilated patients to broader roles in pain management, opioid reduction, and delirium prevention, while facilitating patient cooperation in procedures like awake craniotomy[14]. By reducing sympathetic tone and stabilizing hemodynamics, it potentially supports cerebral perfusion and neuroprotection[6,15], although its direct impact on intracranial pressure remains controversial and appears context- and dose-dependent[16,17]. Recent evidence also highlights variability in its delirium prevention efficacy across clinical settings[18].

Despite some uncertainties, several studies, including our own, have demonstrated dexmedetomidine's neuroprotective potential in acute brain injuries. Our landmark analyses and Kaplan-Meier survival curves further suggest that early dexmedetomidine administration could be associated with improved survival outcomes, indicating possible clinical significance beyond statistical findings. However, further prospective studies are warranted to confirm these observations and to evaluate their potential implications for sedation strategies in ABI patients. By reducing inflammation and apoptosis and stabilizing the blood-brain barrier, dexmedetomidine exerts significant protective effects[13,19–21]. Prior studies similarly reported that early dexmedetomidine exposure significantly reduced hospital mortality and improved recovery metrics in critically ill patients, highlighting its potential benefits in diverse acute brain injury settings[13,20,22,23].

Delirium, a frequent complication in patients with acute brain injuries, is associated with prolonged ICU stays, extended mechanical ventilation, and increased morbidity and mortality[9,24,25]. Effective delirium management is critical for reducing secondary brain injury and promoting recovery. Dexmedetomidine, by alleviating agitation and mitigating complications linked to traditional sedatives, has been shown to reduce delirium incidence and improve outcomes[24,26].

The neuroprotective effects of dexmedetomidine primarily involve modulation of neuroinflammation, oxidative stress, and apoptosis, collectively stabilizing the blood-brain barrier and reducing neuronal injury, delirium, and mortality[27–29]. Specifically, dexmedetomidine attenuates neuroinflammation by suppressing

microglial activation and inflammatory pathways, including NF-κB signaling. As a selective α2AR agonist, it reduces sympathetic overactivation through Gi/o protein-coupled signaling, which helps stabilize systemic inflammation in critically ill patients[29]. It also reduces inflammasome activation and astrocytic complement release, protecting against cognitive dysfunction[30]. Furthermore, dexmedetomidine activates antioxidative pathways (e.g., HIF-1α/HO-1, AMPK/GSK-3β/Nrf2), stabilizes mitochondrial dynamics, reduces oxidative injury and ferroptosis, and suppresses apoptotic signaling (e.g., Bax, caspase-3), promoting neuronal survival and functional recovery[31–33]. These mechanisms support dexmedetomidine's pivotal role in refining sedation practices and improving clinical outcomes for neurocritical patients[6,7,25,34]. Our mediation analyses revealed that delirium substantially mediates the beneficial effects of dexmedetomidine, highlighting delirium prevention as a critical target for optimizing ICU sedation and enhancing clinical outcomes.

However, several limitations should be acknowledged. As a retrospective cohort study, causality cannot be definitively established despite robust statistical adjustments. The reliance on the MIMIC-IV database also comes with inherent limitations, including potential misclassification of diagnoses, reliance on charted medication administration, the absence of detailed documentation of drug-related adverse effects such as hypotension, bradycardia, and fever, and the absence of granular data on the timing and dosing of certain interventions[12,35]. Moreover, unmeasured confounding factors, such as differences in ICU sedation protocols or institutional practices across hospitals, may influence outcomes despite careful statistical adjustment. Additionally, although we adjusted for the use of midazolam, propofol, and ketamine in sensitivity analyses, we did not perform direct comparative effectiveness analyses between dexmedetomidine and these sedatives. This lack of head-to-head comparison limits the ability to fully contextualize dexmedetomidine's specific clinical value relative to alternative sedation strategies. Future prospective comparative trials are necessary to more definitively clarify these relationships and inform optimized sedation protocols in acute brain injury patients.

Conclusion

This study provides strong evidence that dexmedetomidine use in ICU patients with acute brain injury is associated with reduced in-hospital and ICU mortality, as well as improved secondary outcomes, including vasopressor-free and ventilation-free days within 28 days. Mediation analysis further highlighted delirium as a significant mediator of dexmedetomidine's protective effects, accounting for a substantial proportion of its impact on both mortality and ICU-related outcomes. Future research should investigate the comparative efficacy of dexmedetomidine relative to other sedatives, particularly in terms of long-term neurological outcomes, optimal dosing strategies, and its integration into multimodal neuroprotective protocols. Such studies will help refine sedation strategies and further optimize care for patients with ABI.

Data availability

The data that support the findings of this study are openly available in mimiciv at https://physionet.org/content/mimiciv/3.1/

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References

1. Wang, Y. et al. Burden of common neurologic diseases in Asian countries, 1990–2019: an analysis for the global burden of disease study 2019 [J]. *Neurology* **100**(21), e2141–e2154 (2023).
2. Oddo, M. et al. The neurological pupil index for outcome prognostication in people with acute brain injury (ORANGE): a prospective, observational, multicentre cohort study . *Lancet Neurol.* **22**(10), 925–933 (2023).
3. Robba, C. et al. Intracranial pressure monitoring in patients with acute brain injury in the intensive care unit (SYNAPSE-ICU): an international, prospective observational cohort study . *Lancet Neurol.* **20**(7), 548–558 (2021).
4. Krishnamoorthy, V. et al. Multiorgan dysfunction after severe traumatic brain injury: epidemiology, mechanisms, and clinical management . *Chest* **160**(3), 956–964 (2021).
5. Dewan, M. C. et al. Estimating the global incidence of traumatic brain injury . *J. Neurosurg.* **130**(4), 1080–1097 (2019).
6. Bauerschmidt, A. et al. Modern sedation and analgesia strategies in neurocritical care . *Curr. Neurol. Neurosci. Rep.* **23**(4), 149–158 (2023).
7. Patel, M. B. et al. Delirium monitoring in neurocritically ill patients: A systematic review . *Crit. Care Med.* **46**(11), 1832–1841 (2018).
8. LIM, J. et al. Dexmedetomidine for analgesia and sedation in newborn infants receiving mechanical ventilation . *Cochrane Database Syst. Rev.* **5**(5), CD012361 (2024).
9. Rollo, E. et al. Impact of delirium on the outcome of stroke: a prospective, observational, cohort study . *J. Neurol.* **269**(12), 6467–6475 (2022).
10. Zhang, Y. et al. Validity and predictability of the confusion assessment method for the intensive care unit for delirium among critically ill patients in the intensive care unit: A systematic review and meta-analysis . *Nurs. Crit. Care* **29**(6), 1204–1214 (2024).
11. Kabata, D. Prognostic score-based model averaging approach for propensity score estimation . *BMC Med. Res. Methodol.* **24**(1), 228 (2024).
12. Feng, M. et al. Transthoracic echocardiography and mortality in sepsis: analysis of the MIMIC-III database . *Intensive Care Med.* **44**(6), 884–892 (2018).
13. Liu, S. Y. et al. Association of early Dexmedetomidine utilization with clinical outcomes after Moderate-Severe traumatic brain injury: A retrospective cohort study . *Anesth. Analg* **139**(2), 366–374 (2024).
14. Ramaswamy S M et al. Dexmedetomidine-induced deep sedation mimics non-rapid eye movement stage 3 sleep: large-scale validation using machine learning .*Sleep*, ***44****(2).* (2021).
15. Liu, X. et al. Recent advances in the clinical value and potential of Dexmedetomidine . *J. Inflamm. Res.* **14**, 7507–7527 (2021).
16. Kallioinen, M. et al. Cerebral autoregulation after aneurysmal subarachnoid haemorrhage. A preliminary study comparing Dexmedetomidine to Propofol and/or Midazolam . *Acta Anaesthesiol. Scand.* **64**(9), 1278–1286 (2020).
17. Schomer, K. J. et al. Dexmedetomidine for refractory intracranial hypertension . *J. Intensive Care Med.* **34**(1), 62–66 (2019).

18. Turan, A. et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial . *Lancet (London England)* **396**(10245), 177–185 (2020).
19. Veronese, N. et al. Interventions to prevent and treat delirium: an umbrella review of randomized controlled trials . *Ageing Res. Rev.* **97**, 102313 (2024).
20. Yu, Y. et al. Effect of Dexmedetomidine on posttraumatic stress disorder in patients undergoing emergency trauma surgery: A randomized clinical trial. *JAMA Netw. Open.* **6**(6), e2318611 (2023).
21. Li, S. et al. Dexmedetomidine administration during brain tumour resection for prevention of postoperative delirium: a randomised trial . *Br. J. Anaesth.* **130**(2), e307–e316 (2023).
22. Huang, H. et al. The relationship between Dexmedetomidine administration and prognosis in patients with sepsis-induced coagulopathy: a retrospective cohort study . *Front. Pharmacol.* **15**, 1414809 (2024).
23. Shi, X. et al. Effect of different sedatives on the prognosis of patients with mechanical ventilation: a retrospective cohort study based on MIMIC-IV database . *Front. Pharmacol.* **15**, 1301451 (2024).
24. Jin, Z., Hu, J. & Ma, D. Postoperative delirium: perioperative assessment, risk reduction, and management . *Br. J. Anaesth.* **125**(4), 492–504 (2020).
25. Prendergast, N. T., Tiberio, P. J. & Girard, T. D. Treatment of delirium during critical illness. *Annu. Rev. Med.* **73**, 407–421 (2022).
26. Burry, L. et al. Pharmacological interventions for the treatment of delirium in critically ill adults . *Cochrane Database Syst. Rev.* **9**(9), CD011749 (2019).
27. Hu, Y. et al. The neuroprotective effect of Dexmedetomidine and its mechanism . *Front. Pharmacol.* **13**, 965661 (2022).
28. Yaman, E. et al. Evaluation of topical Dexmedetomidine administration in postlaminectomy epidural fibrosis rat model . *Int. J. Surg.* **53**, 80–85 (2018).
29. Yuan, D. et al. Activation of the α2B adrenoceptor by the sedative sympatholytic dexmedetomidine . *Nat. Chem. Biol.* **16**(5), 507–512 (2020).
30. Zhai, Q. et al. Reducing complement activation during sleep deprivation yields cognitive improvement by Dexmedetomidine . *Br. J. Anaesth.* **131**(3), 542–555 (2023).
31. Shi, J. et al. Dexmedetomidine ameliorates endotoxin-induced acute lung injury in vivo and in vitro by preserving mitochondrial dynamic equilibrium through the HIF-1a/HO-1 signaling pathway . *Redox Biol.* **41**, 101954 (2021).
32. Wang, Z. et al. Dexmedetomidine attenuates myocardial ischemia/reperfusion-induced ferroptosis via AMPK/GSK-3β/Nrf2 axis . *Biomed. Pharmacother* **154**, 113572 (2022).
33. Hou, M. et al. Dexmedetomidine against intestinal ischemia/reperfusion injury: A systematic review and meta-analysis of preclinical studies . *Eur. J. Pharmacol.* **959**, 176090 (2023).
34. Li, Y. et al. Promising effects of montelukast for critically Ill asthma patients via a reduction in delirium *Pharmaceuticals (Basel)***17**(1), (2024).
35. Wu, W.-T. et al. Data mining in clinical big data: the frequently used databases, steps, and methodological models . *Mil Med. Res.* **8**(1), 44 (2021).

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Author contributions

W and S wrote the main manuscript text. L and Y were responsible for data analysis and statistics. W and Z prepared Tables 1 and 2. W and H created Figures 1–3. Li assisted with study design and literature review. All authors reviewed the manuscript and provided feedback.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was performed according to the guidelines of the Helsinki Declaration. The use of the MIMIC-IV database was approved by the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The data is publicly available (in the MIMIC-IV database), therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Additional information

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