

# Effect of midazolam on delirium in critically ill patients: a propensity score analysis

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## Abstract

**Objective:** To observe the association between exposure to midazolam within 24 hours prior to delirium assessment and the risk of delirium.

**Methods:** We performed a systematic cohort study with two sets of cohorts to estimate the relative risks of outcomes among patients administered midazolam within 24 hours prior to delirium assessment. Propensity score matching was performed to generate a balanced 1:1 matched cohort and identify potential prognostic factors. The outcomes included the odds of delirium, mortality, length of intensive care unit stay, length of hospitalization, and odds of being discharged home.

**Results:** A total of 78,364 patients were included in this study, of whom 22,159 (28.28%) had positive records. Propensity matching successfully balanced covariates for 9348 patients (4674 per group). Compared with no administration of midazolam, midazolam administration was associated with a significantly higher risk of delirium, higher mortality, and a longer intensive care unit stay. Patients treated with midazolam were relatively less likely to be discharged home. There was no significant difference in hospitalization duration.

**Conclusions:** Midazolam may be an independent risk factor for delirium in critically ill patients.

## Keywords

Midazolam, delirium, critical care, propensity score analysis, cohort study, risk factor

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## Introduction

Delirium is a syndrome characterized by the acute onset of cerebral dysfunction with a change or fluctuation in mental status, inattention, and either disorganized thinking or an altered level of consciousness.<sup>1-4</sup> Delirium in patients over the age of 65 years is estimated to cost more than \$164 billion per year in the United States.<sup>5</sup> With the government considering limiting payments for delirium, aggressive efforts are needed to reduce all factors contributing to this condition.<sup>6</sup>

Midazolam is still frequently used for sedation because of its limited effect on hemodynamics and short half-life,<sup>7-9</sup> despite clinical practice guidelines describing that benzodiazepine use is a modifiable risk factor for delirium in critically ill adults with strong supporting evidence.<sup>10</sup> However, real-world evidence of the relative effectiveness of midazolam and its associations with delirium in critically ill patients is lacking.

Based on the common use of midazolam for the sedation of patients admitted to the intensive care unit (ICU), we performed a retrospective, multicenter, observational cohort study to investigate the relationship between midazolam administration within 24 hours prior to delirium assessment and the incidence of delirium in patients in the ICU and patient-centered outcomes.

## Materials and methods

### *Ethics statement*

Consent was obtained for the original data collection, and the institutional review boards of the Massachusetts Institute of Technology (Cambridge, MA, USA) approved the establishment of the database. Therefore, the need for ethical approval and informed consent was waived for this manuscript.

## Data source

Study data were derived from three electronic databases. The Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) III (version 1.4) Database,<sup>11</sup> Medical Information Mart for Intensive Care (MIMIC) IV (version 0.4) Database,<sup>12</sup> and eICU Collaborative Research Database<sup>13</sup> are maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology.

### *Study population and stratification*

All patient details have been deidentified. The study population included all patients who underwent delirium assessment after admission to the ICU. For patients with multiple positive values, we included only the first episode. If all assessment results were negative, we selected only the first assessment. The variables chosen for each patient were collected only once. Patients who received midazolam or not within 24 hours before the diagnosis of delirium were observed. We performed a cohort study, and patients were enrolled into two cohorts: midazolam and no midazolam.

The inclusion criteria in this study were as follows: (1) for patients with multiple ICU stays, only the first ICU stay was eligible; (2) adults received midazolam at ICU admission; (3) ICU stay  $\geq 24$  hours; and (4) delirium assessment.

### *Outcomes*

The primary outcome was the odds ratio (OR) of delirium, and secondary outcomes included hospital mortality, ICU length of stay, hospitalization duration, and discharge destination (home versus elsewhere).

## Data analysis

Patient characteristics included age, sex, ethnicity, acute physiology and chronic health evaluation (APACHE) III score, Glasgow Coma Scale, mean blood pressure, respiratory rate, urine volume, hemoglobin, white blood cell count, alanine transaminase, glutamic oxaloacetic transaminase, albumin, blood urea nitrogen, creatinine, lactate, oxygenation index, mechanical ventilation, and hospital characteristics. The APACHE-III scoring system is designed to prospectively predict mortality in individual patients in the ICU.<sup>14</sup> Hospital characteristics, including ICU type, number of ICU beds, and teaching status, were defined according to the database.

Descriptive data are presented as the medians (25th to 75th percentiles) for continuous variables and frequencies (%) for categorical variables. Categorical variables were compared between groups using the chi-square test. Unpaired t-tests or Kruskal–Wallis tests were used for continuous variables.

Propensity score generation, stratification by deciles, and 1:1 matching between groups were performed using the R package MatchIt.<sup>15</sup> A non-parsimonious regression model was used to produce a propensity score for the group with fewer patients using the patient characteristics described above. For the propensity score analysis (our primary analysis), each patient in the group with fewer patients was matched to their nearest neighbor with a score within 0.001. We chose to match to the third decimal point (a caliper of 0.001) because this value is less than 0.02 standard deviations of the propensity score, which is a commonly suggested range. Estimating the propensity score using a logit model resulted in both reasonable matches and an appropriate overall sample size. An unpaired t-test was used before propensity

matching, and a paired t-test was used after matching. The final models included the hospital as a random effect, and all patient characteristics were used to calculate the propensity score. Additionally, multivariable regression modeling, including all patient characteristics used to calculate the propensity score, was performed to confirm these findings (secondary analysis). All analyses were performed using R version 4.0.3 ([www.r-project.org](http://www.r-project.org)).

## Results

A total of 46,428 patients in the ICU and 61,051 ICU admissions in the MIMIC-III database v1.4, 50,048 patients in the ICU and 69,619 ICU admissions in the MIMIC-IV database v0.4, and 177,863 patients in the ICU and 626,858 ICU admissions in the eICU Collaborative Research Database were available (Supplementary Table 1). Of these, 621,189 sequential delirium assessment records were available. Finally, 78,364 (28.56%) patients were included in this study. We identified 22,159 (28.28%) patients with positive records. Missing data were imputed with the multivariate imputation using the chain equations (MICE) method.<sup>16</sup> The amount of missing data was low.

A total of 4808 patients received midazolam within 24 hours of admission. Before propensity score matching, there were statistically significant differences in age and ethnicity in the stratified analyses between the midazolam and no midazolam groups. Overall, compared with patients in the no midazolam group, patients in the midazolam group were less likely to be women ( $P < 0.001$ ) and had a higher APACHE-III score ( $P < 0.001$ ). However, patients who received midazolam had higher blood urea nitrogen ( $P < 0.001$ ) and white blood cell count ( $P < 0.001$ ) values but lower mean blood pressure ( $P < 0.001$ ), hemoglobin

( $P < 0.001$ ), alanine transaminase ( $P < 0.001$ ), glutamic oxaloacetic transaminase ( $P < 0.001$ ), and albumin ( $P < 0.001$ ) values than those who did not receive midazolam. Moreover, patients in the midazolam group had higher rates of mechanical ventilation ( $P < 0.001$ ) and a higher oxygenation index ( $P < 0.001$ ) than those in the no midazolam group (Table 1).

### **Propensity-matched analysis**

After propensity matching, 97% of patients in the midazolam group were successfully matched 1:1 with an equal number of patients in the no midazolam group, yielding a total of 4674 patients in each group. Propensity matching eliminated differences between patients and clinical variables and reduced differences in hospital characteristics. After matching, the baseline characteristics were balanced, as shown in Table 1.

In the fully adjusted, propensity score-matched cohorts, patients treated with midazolam exhibited a significant difference in the odds of delirium (OR, 2.54; 95% confidence interval [CI], 2.31–2.79;  $P < 0.001$ ) compared with patients who were not treated with midazolam. Moreover, patients who used midazolam had higher odds of mortality (OR, 1.33; 95% CI, 1.17–1.52;  $P < 0.001$ ), more ICU days (0.37; 95% CI, 0.29–0.45;  $P < 0.001$ ), and lower odds of being discharged home (OR, 0.81; 95% CI, 0.74–0.89;  $P < 0.001$ ) than patients who did not use midazolam. However, there were no significant differences in the hospital length of stay between the two groups (Table 2).

### **Multivariable analysis**

The entire cohort (78,364 patients) was then analyzed using multivariable regression after adjusting for differences in the patient and hospital characteristics used to calculate the propensity score. This multivariable analysis demonstrated that patients treated

with midazolam exhibited significant differences in the odds of delirium (OR, 3.04; 95% CI, 2.83–3.26;  $P < 0.001$ ) and mortality rate (OR, 1.30; 95% CI, 1.18–1.43;  $P < 0.001$ ) compared with patients who were not treated with midazolam. However, patients treated with midazolam had longer ICU stays (0.54; 95% CI, 0.50–0.57;  $P < 0.001$ ) but similar hospital stays (–0.03; 95% CI, –0.30 to 0.23) than patients who were not treated with midazolam. Finally, patients who were not treated with midazolam had an increased likelihood of being discharged home than patients treated with midazolam (0.79; 95% CI, 0.73–0.84;  $P < 0.001$ ) (Table 2).

## **Discussion**

Using three large databases, MIMIC III v1.4, MIMIC-IV v0.4, and eICU Collaborative Research, we performed a multicenter, observational cohort study to assess outcomes in patients at risk for delirium who were treated with midazolam infusions within 24 hours before delirium diagnoses were defined. We observed that delirium was diagnosed in 28.28% of patients, and patients who used midazolam within 24 hours before diagnosis were more likely to develop delirium. Moreover, our data show that midazolam was associated with multiple detrimental outcomes, including an increased risk of mortality, longer ICU stays, and lower likelihood of being discharged. However, there was no significant association between treatment with midazolam and hospitalization length.

Clinical practice guidelines mention that benzodiazepine use is a modifiable factor, with strong evidence for an association with delirium detected by screening tools.<sup>10</sup> Recently, published meta-analyses have demonstrated that midazolam was associated with a significantly higher rate of delirium.<sup>17,18</sup> These studies were limited by small sample sizes and limited long-term

**Table 1.** Baseline characteristics of the patients.

Clinical variable*	Before propensity matching		SD#	P value	After propensity matching		SD	P value
	Midazolam (N=4808)	No Midazolam (N=73,556)			Midazolam (N=4674)	No Midazolam (N=4674)		
Age, No. (%)								
18 to 45 years	945 (19.7)	9,582 (13)	0.261	<0.001	1,018 (18.7)	767 (19.7)	0.033	0.65
46 to 65 years	1,876 (39)	25,641 (34.9)			2,164 (39.7)	1,527 (39.2)		
66 to 80 years	1,404 (29.2)	24,495 (33.3)			1,644 (30.1)	1,073 (27.6)		
81 to 89 years	458 (9.5)	10,342 (14.1)			500 (9.2)	409 (10.5)		
over 89 years	125 (2.6)	3,496 (4.8)			129 (2.4)	117 (3)		
Women, No. (%)	2,002 (41.6)	33,697 (45.8)	0.084	<0.001	2,206 (40.4)	1,701 (43.7)	0.002	0.933
Ethnicity, No. (%)								
White	2,940 (61.1)	50,421 (68.5)	0.272	<0.001	3,286 (60.2)	2,488 (63.9)	0.016	0.964
Black	542 (11.3)	9,572 (13)			596 (10.9)	453 (11.6)		
Latino	173 (3.6)	3,253 (4.4)			199 (3.6)	146 (3.8)		
Asian	121 (2.5)	1,850 (2.5)			143 (2.6)	98 (2.5)		
Other	1,032 (21.5)	8,460 (11.5)			1,231 (22.6)	708 (18.2)		
APACHE-III score	51 (36-72)	38 (28-52)	0.595	<0.001	51 (36-74)	47 (34-67)	0.035	0.087
Glasgow Coma Scale	15 (13-15)	13.2 (13-15)	0.003	0.812	15 (14-15)	14 (13-15)	0.003	0.866
Mean blood pressure, mmHg	80.3 (71.3-91.7)	85.4 (75.3-93.5)	0.193	<0.001	78.3 (70.3-88.7)	84.7 (74.7-95.3)	0.002	0.919
Respiratory rate, beats per minute	19 (16-23)	19 (16.5-22)	0.063	<0.001	19 (16-22)	19.4 (16.5-22.9)	0.016	0.433
Urine volume, mL/kg/hour	1.1 (0.7-1.5)	1.1 (0.7-1.5)	0.002	0.9	1.1 (0.7-1.5)	1.1 (0.7-1.5)	0.012	0.553
Hemoglobin, g/dL	10.7 (9-11.7)	10.9 (9.7-11.8)	0.169	<0.001	10.5 (9-11.6)	10.9 (9.3-11.6)	0.005	0.793
White blood cell, K/ $\mu$ L	11.6 (8.1-15.2)	11.3 (8.7-13.7)	0.086	<0.001	12 (8.7-15.9)	11.1 (8.1-13.8)	0.009	0.655
Alanine transaminase, IU/L	67.9 (23-100.9)	74.1 (26-96.8)	0.095	<0.001	68.3 (22-100.4)	75.7 (26-104.9)	0.008	0.696
Glutamic oxaloacetic transaminase, IU/L	90.6 (33-144.1)	99.3 (31-136.8)	0.112	<0.001	90 (33-142.8)	101 (37-147.1)	0.012	0.566
Albumin, g/dL	3.1 (2.8-3.4)	3.3 (3-3.5)	0.265	<0.001	3.1 (2.8-3.4)	3.2 (2.9-3.4)	0.028	0.181
Blood urea nitrogen, mg/dL	21 (13-34)	20 (15-29)	0.093	<0.001	20.9 (14-33.6)	21 (14-31)	0.015	0.458
Creatinine, mg/dL	1 (0.7-1.6)	1.1 (0.8-1.4)	0.029	0.052	1 (0.7-1.6)	1.1 (0.7-1.5)	0.02	0.322
Lactate, mg/dL	1.7 (1.3-2.1)	1.8 (1.5-2.2)	0.019	0.136	1.7 (1.3-2.2)	1.7 (1.4-2.1)	0.016	0.427
Oxygenation index	54.7 (50-60.4)	51.9 (50.6-57.3)	0.717	<0.001	53.9 (50-60)	55.9 (50.8-60.9)	0.045	0.03
Mechanical ventilation, No. (%)	3,134 (65.2)	13,534 (18.4)	1.077	<0.001	3,000 (64.1)	2,952 (63.1)	0.021	0.312

(continued)

Table 1. Continued.

Clinical variable*	Before propensity matching		SD#	P value	After propensity matching		SD	P value
	Midazolam (N=4808)	No Midazolam (N=73,556)			Midazolam (N=4674)	No Midazolam (N=4674)		
ICU type, No. (%)								
SICU	227 (4.7)	3,462 (4.7)	0.399	<0.001	213 (3.9)	230 (5.9)	0.065	0.02
CCU	126 (2.6)	6,678 (9.1)			112 (2.1)	107 (2.7)		
NICU	10 (0.2)	3,000 (4.1)			7 (0.1)	5 (0.1)		
Others	4,445 (92.5)	60,416 (82.1)			5,123 (93.9)	3,551 (91.2)		
Number of beds, No. (%)								
<100	0 (0)	470 (0.6)	0.508	<0.001	0 (0)	0 (0)	0.073	0.002
100–249	74 (1.5)	5,477 (7.4)			55 (1)	65 (1.7)		
250–499	85 (1.8)	7,762 (10.6)			55 (1)	87 (2.2)		
≥500	4,649 (96.7)	59,847 (81.4)			5,345 (98)	3,741 (96.1)		
Teaching, No. (%)	4,586 (95.4)	56,129 (76.3)	0.569	<0.001	5,268 (96.6)	3,703 (95.1)	0.073	0.001

\*Data shown as the mean ± standard deviation, number (percent), or median (interquartile range) as appropriate.

#SD = standardized difference (SD 0.1 represents significant differences in covariables between groups).

APACHE-III score, the acute physiology and chronic health evaluation III score; CCU, cardiac care unit; NICU, neurological intensive care unit; SICU, surgical intensive care unit.

**Table 2.** Results of propensity-matched and multivariate analysis in patients with midazolam treatment.

	Propensity matched analysis (N=9348)			Multivariable analysis (N=78,364)		
	Estimate	95% CI	P value	Estimate	95% CI	P value
Odds of delirium, OR	2.54	2.31 to 2.79	<0.001	3.04	2.83 to 3.26	<0.001
Odds of mortality, OR	1.33	1.17 to 1.52	<0.001	1.30	1.18 to 1.43	<0.001
Difference in ICU days	0.37	0.29 to 0.45	<0.001	0.54	0.50 to 0.57	<0.001
Difference in hospital days	-0.35	-0.66 to -0.04	0.03	-0.03	-0.30 to 0.23	0.81
Odds of discharge to home, OR	0.81	0.74 to 0.89	<0.001	0.79	0.73 to 0.84	<0.001

OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

observations. Another propensity score-matched cohort study showed that midazolam-dominant sedation strategies were associated with an increased delirium risk, mortality, length of ICU stay, and hospital days.<sup>19</sup> Unfortunately, they did not test the isolated effects of midazolam and eliminate the influence of midazolam metabolism and clearance, whereas our study did. Additionally, a single-center analysis showed that benzodiazepine administration in an awake patient without delirium was associated with an increased risk of delirium the next day.<sup>20</sup> However, a multicenter systematic comparison of the effectiveness and safety of midazolam within 24 hours prior to delirium assessment in patients in the ICU has been lacking.

There are multiple mechanisms by which midazolam may increase delirium. Midazolam activates  $\gamma$ -aminobutyric acid A (GABA<sub>A</sub>) neuronal receptors in the brain, and their activation can alter the levels of numerous neurotransmitters, such as dopamine, serotonin, acetylcholine, norepinephrine, and glutamate, which are believed to be deliriogenic.<sup>21-23</sup> Midazolam may be involved in the pathogenesis of delirium through overstimulation of the cortical GABA system, thereby reducing corticostriatal glutamatergic tone and ultimately impairing the filtering action of the thalamus, leading to confusion or psychosis.<sup>24</sup> In addition to altering

neurotransmitter concentrations, midazolam may generate more central nervous system inhibitory effects at higher doses<sup>25</sup> and impair the quality of sleep via slow-wave sleep suppression, possibly contributing to delirium.<sup>23,26</sup> Furthermore, midazolam alters sleep patterns and increases the risk of circadian disruption and delirium in humans.<sup>27,28</sup> We did not pool more risk factors for delirium but presented results from each pre-collected item separately. Our authors independently screened and extracted data using a prespecified data extraction scheme, a process intended to reduce bias during data collection.

Delirium may increase mortality, which is not directly related to midazolam administration. Midazolam use was found to be a risk factor for delirium after liver transplantation in a systematic review and meta-analysis, which also showed that delirium was a mortality risk factor according to the pooled results of ICU mortality.<sup>18</sup> Similarly, a multicenter, retrospective, cohort study by Lonardo et al. demonstrated higher mortality in patients managed with benzodiazepines than in those administered propofol. They postulated that the mortality effect of midazolam might be due to increased rates of delirium,<sup>29</sup> and some evidence supports that delirium is associated with substantial morbidity both during and after ICU admission.<sup>30-32</sup> Each additional day of delirium increases the hazard



of mortality by 10% and increases the likelihood of a poor functional status at 3 and 6 months.<sup>33–36</sup>

Our study has three strengths. First, this retrospective cohort study included a relatively large population and accurately measured clinical variables in an actual clinical setting in a large number of ICUs. Acknowledging the possibility of confounding, we used propensity score-matched analysis to balance measured pretreatment variables that may influence the effect and impact the outcomes. Second, it is important to use time-dependent multivariable analysis methods given that disease severity, midazolam administration, and delirium occurrence frequently oscillate over the course of the ICU stay. We ensured that medical treatment was provided within 24 hours before the delirium assessment to limit the influence of other confounding factors. Third, this study used data from multiple ICU databases across a range of hospital and ICU settings, which made our results accurately reflect the outcomes observed in an actual clinical practice environment.

Several limitations of this study warrant discussion. First, this is an observational study; thus, causal associations cannot be determined. Second, there were some missing data for multiple confounding variables, and some variables, such as drug doses, target sedation levels, treatment durations, or daily data on sedation levels, could not be effectively merged or compared. Bias may still exist despite the use of propensity score matching and regression modeling to control for a variety of patient and hospital confounders. Third, we could not exclude, measure, or control for the use of intermittent midazolam dosing given on an as-needed basis. We could exclude only patients administered other sedative drugs, such as opioid drugs or propofol, to ensure that they received the same medication. Fourth, our study was a retrospective

cohort study based on electronic healthcare records, and the data were generated during routine clinical visits. Because the MIMIC-III data ranged from 2001 to 2015, eICU Collaborative Research data ranged from 2014 to 2015, and MIMIC-IV data ranged from 2018 to 2019, our results were adjusted for the admission period.

## Conclusions

Patients who use midazolam within 24 hours before the diagnosis of delirium may be more susceptible to developing delirium, and they may have higher odds of mortality, more ICU days, and lower odds of discharge than those who are not treated with midazolam. Further studies are needed to evaluate the mechanism underlying these differences and validate these findings in other cohorts of patients.

## Data availability statement

The three databases used in this research, MIMIC-III, MIMIC IV, and eICU, are available for access, in part or in full, by relevant parties subject to abiding by their usage policies. To facilitate the reproduction of our results, we shall make fully anonymized data available on the figshare from the publication of this manuscript (<https://figshare.com/s/6ffd470721a04b7b9ca3>). Additionally, interested researchers can contact Mr. Hu by email ([anmin.edu@gmail.com](mailto:anmin.edu@gmail.com)) for more detailed information.

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## Declaration of conflicting interest

The authors declare that they have no competing interests.

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## Author contributions

HJS and AMH conceived and designed the study. AMH and HJS acquired the data. HJS, RXY, and AMH analyzed and interpreted the data. HJS and RXY drafted the manuscript. AMH and JZZ critically revised the manuscript for valuable intellectual content. AMH, HJS, and JHC performed the statistical analysis. All authors read and approved the final manuscript.

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## Supplemental material

Supplemental material for this article is available online.

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