

# Midazolam Increases The Risk of Delirium In Critically Ill Patients: A Propensity Score Analysis.

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## Research Article

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# Abstract

**BACKGROUND:** Midazolam is commonly administered in the intensive care unit (ICU) because of its limited effect on hemodynamics and stable calming and sleep-induction effects. Recent concerns about an increased risk of delirium associated with midazolam have resulted in decreased midazolam usage in the ICU. However, whether midazolam administration within 24 hours prior is related to the occurrence of delirium is still unknown.

**METHODS:** We used real-world data from MIMIC III v1.4, MIMIC-IV v0.4 and eICU Collaborative Research to perform comparisons and assess the associated outcome effectiveness. We performed a systematic study with two 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 to identify potential prognostic factors. The outcomes included mortality, length of ICU stay, length of hospitalization, and odds of being discharged home.

**RESULTS:** Propensity matching successfully balanced covariates for 9,348 patients (4,674 per group). There was no significant difference in hospitalization duration, ( $P=0.03$ ). However, compared to no administration of midazolam, midazolam administration was associated with a significantly higher risk for delirium ( $P<0.001$ ). When compared with no midazolam administration, the use of midazolam, was associated with higher mortality and a longer ICU stay ( $P<0.001$ ). Patients treated with midazolam were relatively less likely to be discharged home ( $P<0.001$ ).

**CONCLUSIONS:** Compared with no administration of midazolam, midazolam administration was associated with a difference in the incidence of delirium, mortality, ICU stay and likelihood of being discharged home but was not associated with hospitalization duration. These data suggest that midazolam may not be the preferred sedative drug for patients at risk for delirium.

## Background

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 [1–4]. Delirium in patients over the age of 65 years is estimated to cost more than \$164 billion per year in the US [5]. With the government considering limiting payments for delirium, aggressive effort is needed to reduce all factors contributing to this condition [6].

Midazolam is still frequently used for sedation because of its limited effect on hemodynamics and its short half-life [7–9], despite clinical practice guidelines describing that benzodiazepine use is a modifiable risk factor for delirium in critically ill adults with strong supporting evidence [10]. 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 sedation of intensive care unit (ICU) patients, 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 the ICU patients and patient-centered outcomes. This systematic study might improve delirium prevention.

## Methods

### Data source

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

### Study population and stratification

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 of the assessment results were negative, we also selected only the first assessment. The relevant data for each patient were collected only once. Patients who received midazolam or not within 24 hours before the diagnosis of delirium were observed. Patients were enrolled into two cohorts: midazolam vs. 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  $\geq 18$  years of age at ICU admission; (3) ICU stay  $\geq 24$  hours; and (4) delirium assessment.

## Outcomes

The primary outcome was the odds 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 (GCS), mean blood pressure (MBP), 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 ICU patients [14]. 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 Match It [15]. A nonparsimonious 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 the third decimal point (a caliper of 0.001) because this value is less than 0.02 SDs 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. 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 the patient characteristics used to calculate the propensity score, was performed to confirm these findings (secondary analysis).

Missing data were imputed with the multivariate imputation by chain equations (MICE) method [16]. The amount of missing data was low. All analyses were performed using R version 4.0.3.

## Results

A total of 46,428 ICU patients and 61,051 ICU admissions in the MIMIC-III database v1.4, 50,048 ICU patients and 69,619 ICU admissions in the MIMIC-IV database v0.4, and 177,863 ICU patients and 626,858 ICU admissions in the eICU Collaborative Research Database were available. Of these, a total of 621,189 sequential delirium assessment records were available. Finally, 78,364 patients were included in this study. We identified 22,159 (28.28%) patients with positive records.

A total of 4,808 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 group. Overall, compared with patients in the no midazolam group, patients in the midazolam group were less likely to be female (41.6 vs. 45.8%;  $P < 0.001$ ) and had a higher APACHE-III score (median [interquartile range], 51 [13–15] vs. 38 [28–52];

$P < 0.001$ ). However, patients who received midazolam had higher values of blood urea nitrogen (BUN) (21 [13–34] vs. 20 [15–29];  $P < 0.001$ ) and white blood cell count (WBC) (11.6 [8.1–15.2] vs. 11.3 [8.7–13.7];  $P < 0.001$ ) but lower values of mean blood pressure (MBP) (80.3 [71.3–91.7] vs. 85.4 [75.3–93.5];  $P < 0.001$ ), hemoglobin (Hb) (10.7 [9–11.7] vs. 10.9 [9.7–11.8];  $P < 0.001$ ), alanine transaminase (ALT) (67.9 [23–100.9] vs. 74.1 [26–96.8];  $P < 0.001$ ), glutamic oxaloacetic transaminase (GOT) (90.6 [33–144.1] vs. 99.3 [31–136.8];  $P < 0.001$ ) and albumin (3.1 [2.8–3.4] vs. 3.3 [3–3.5];  $P < 0.001$ ) than those who did not receive midazolam. Moreover, patients in the midazolam group had higher rates of mechanical ventilation (65.2 vs. 18.4%;  $P < 0.001$ ) and a higher oxygenation index (54.7 [50–60.4] vs. 51.9 [50.6–57.3];  $P < 0.001$ ) 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 4,674 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 odds of delirium (odds ratio [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 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 days (-0.03; 95% CI, -0.30 to 0.23;  $P = 0.81$ ) 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 the 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 to home. However, there was no significant association between treatment with midazolam and length of hospitalization.

Recently, published meta-analyses have demonstrated that midazolam was associated with a significantly higher rate of delirium [17, 18]. These studies were limited by small sample sizes and limited long-term observations. Another propensity score-matched cohort study showed that midazolam-dominant sedation strategies were associated with increased delirium risk, mortality, ICU length of stay and hospital days [19]; unfortunately, they did not test the isolated effects of midazolam and eliminate the influence of midazolam metabolism and clearance, while 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 [20]. However, a multicenter systematic comparison of the effectiveness and safety of midazolam within 24 hours prior to delirium assessment in ICU patients 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 [21–23]. Midazolam could indeed be involved in delirium pathogenesis through overstimulation of the cortical GABA system, thereby reducing corticostriatal glutamatergic tone and ultimately hampering the filtering action of the thalamus, leading to confusion or psychosis [24]. In addition to altering neurotransmitter concentrations, midazolam may generate more central nervous system inhibitory effects at higher doses [25] and impair the quality of sleep via slow-wave sleep suppression, thus, possibly contributing to delirium [23, 26]. Moreover, a recent animal study demonstrated that midazolam or inflammation, which downregulate brain PER2 levels, led to significant hippocampus-dependent cognitive deficits, as observed in some types of delirium [27]. The hippocampus appears to play a critical role in the pathogenesis of delirium in humans [28]. Furthermore, midazolam alters sleep patterns and increases the risk of circadian disruption and delirium in humans [29, 30].

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 [18]. Similarly, a multicenter, retrospective, cohort study by Lonardo et al demonstrated higher mortality in patients managed with benzodiazepines compared with those administered propofol. They postulated that midazolam's mortality effect might be due to increased rates of delirium [31], and some evidence supports that delirium is associated with substantial morbidity both during and after ICU admission [32–34]. 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 [35–38].

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 seen in an actual practice environment.

Several limitations of this study warrant discussion. First, this is an observational study, and 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 those patients who were 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. Since the MIMIC-III data ranged from 2001 to 2015, eICU Collaborative Research data ranged from 2014-2015 and MIMIC-IV data ranged from 2018-2019, our results were adjusted for the admission period.

## Conclusion

Patients who used midazolam within 24 hours before the diagnosis of delirium were more susceptible to developing delirium, and they had higher odds of mortality, more ICU days, and lower odds of discharge to home than those who were not treated with midazolam. Therefore, we suggest that clinicians avoid administering midazolam to patients who are scheduled to be

admitted to the ICU. Further studies are needed to evaluate the mechanism underlying these differences and to validate these findings in other cohorts of patients.

## Abbreviations

ICU intensive care unit

MIMIC-III Multiparameter Intelligent Monitoring in Intensive Care III

MIMIC-IV Medical Information Mart for Intensive Care IV

APACHE-III Acute Physiology and Chronic Health Evaluation III

GCS Glasgow Coma Scale

MBP Mean Blood Pressure

MICE Multivariate Imputation by Chain Equations

BUN Blood Urea Nitrogen

WBC White Blood Cell

Hb hemoglobin

ALT Alanine Transaminase

GOT Glutamic Oxaloacetic Transaminase

OR Odds Ratio

CI Confidence Interval

GABA<sub>A</sub>  $\gamma$ -aminobutyric Acid A

## Declarations

### 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 ethical approval statement and informed consent were waived for this manuscript.

### DATA AVAILABILITY STATEMENT

The three databases used in this research, MIMIC-III, MIMIC IV and eICU are available for access, in part or in total, 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 researcher can contact Mr. Hu email ([anmin.edu@gmail.com](mailto:anmin.edu@gmail.com)) for more detailed information.

### COMPETING INTERESTS

The authors declare that they have no competing interests.

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#### AUTHORS' CONTRIBUTIONS

HJS and AMH conceived and designed the study. AMH and HJS and 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 statistical analysis. All authors read and approved the final manuscript.

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#### MATERIAL AND CORRESPONDENCE

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## Tables

**TABLE 1** | Baseline characteristics of the patients.

| Clinical Variable*                | Baseline covariates of patient before Propensity Matching |                         |       |        | Baseline covariates of patient after Propensity Matching |                        |       |        |
|-----------------------------------|---|-------------------------|-------|--------|--|------------------------|-------|--------|
|                                   | Midazolam (N=4,808)                                       | No Midazolam (N=73,556) | SD#   | Pvalue | Midazolam (N=4,674)                                      | No Midazolam (N=4,674) | SD    | Pvalue |
| <b>Age, No. (%)</b>               |   |                         |       |        |  |                        |       |        |
| 18 to 45 years                    | 945 (19.7)  | 9582 (13)               | 0.261 | <0.001 | 1018 (18.7)  | 767 (19.7)             | 0.033 | 0.65   |
| 46 to 65 years                    | 1876 (39)   | 25641 (34.9)            |       |        | 2164 (39.7)  | 1527 (39.2)            |       |        |
| 66 to 80 years                    | 1404 (29.2)   | 24495 (33.3)            |       |        | 1644 (30.1)  | 1073 (27.6)            |       |        |
| 81 to 89 years                    | 458 (9.5)   | 10342 (14.1)            |       |        | 500 (9.2)  | 409 (10.5)             |       |        |
| over 89 years                     | 125 (2.6)   | 3496 (4.8)              |       |        | 129 (2.4)  | 117 (3)                |       |        |
| <b>Female, No. (%)</b>            | 2002 (41.6)   | 33697 (45.8)            | 0.084 | <0.001 | 2206 (40.4)  | 1701 (43.7)            | 0.002 | 0.933  |
| <b>Ethnicity, No. (%)</b>         |   |                         |       |        |  |                        |       |        |
| White                             | 2940 (61.1)   | 50421 (68.5)            | 0.272 | <0.001 | 3286 (60.2)  | 2488 (63.9)            | 0.016 | 0.964  |
| Black                             | 542 (11.3)  | 9572 (13)               |       |        | 596 (10.9)   | 453 (11.6)             |       |        |
| Latino                            | 173 (3.6)   | 3253 (4.4)              |       |        | 199 (3.6)  | 146 (3.8)              |       |        |
| Asian                             | 121 (2.5)   | 1850 (2.5)              |       |        | 143 (2.6)  | 98 (2.5)               |       |        |
| Other                             | 1032 (21.5)   | 8460 (11.5)             |       |        | 1231 (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, Beat 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                          | 90.6 (33-   | 99.3 (31-               | 0.112 | <0.001 | 90 (33-  | 101 (37-               | 0.012 | 0.566  |

|                                 |                |                  |       |        |                |                  |       |       |
|---------------------------------|----------------|------------------|-------|--------|----------------|------------------|-------|-------|
| Oxaloacetic Transaminase, IU/L  | 144.1)         | 136.8)           |       |        | 142.8)         | 147.1)           |       |       |
| 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. (%) | 3134 (65.2)    | 13534 (18.4)     | 1.077 | <0.001 | 4452 (81.6)    | 1500 (38.5)      | 0.021 | 0.312 |
| <b>ICU type, No. (%)</b>        |                |                  |       |        |                |                  |       |       |
| SICU                            | 227 (4.7)      | 3462 (4.7)       | 0.399 | <0.001 | 213 (3.9)      | 230 (5.9)        | 0.065 | 0.02  |
| CCU                             | 126 (2.6)      | 6678 (9.1)       |       |        | 112 (2.1)      | 107 (2.7)        |       |       |
| NICU                            | 10 (0.2)       | 3000 (4.1)       |       |        | 7 (0.1)        | 5 (0.1)          |       |       |
| Others                          | 4445 (92.5)    | 60416 (82.1)     |       |        | 5123 (93.9)    | 3551 (91.2)      |       |       |
| <b>Number of beds, No. (%)</b>  |                |                  |       |        |                |                  |       |       |
| <100                            | 0 (0)          | 470 (0.6)        | 0.508 | <0.001 | 0 (0)          | 0 (0)            | 0.073 | 0.002 |
| 100-249                         | 74 (1.5)       | 5477 (7.4)       |       |        | 55 (1)         | 65 (1.7)         |       |       |
| 250-499                         | 85 (1.8)       | 7762 (10.6)      |       |        | 55 (1)         | 87 (2.2)         |       |       |
| ≥500                            | 4649 (96.7)    | 59847 (81.4)     |       |        | 5345 (98)      | 3741 (96.1)      |       |       |
| Teaching, No. (%)               | 4586 (95.4)    | 56129 (76.3)     | 0.569 | <0.001 | 5268 (96.6)    | 3703 (95.1)      | 0.073 | 0.001 |

Abbreviations: AaDO<sub>2</sub>, alveolar-arterial oxygen difference; APACHE-III score, the acute physiology and chronic health evaluation III score; CCU, cardiac care unit; Dex, dexmedetomidine; NICU, neurological intensive care unit; SICU, surgical intensive care unit.

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

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

**Table2.** Results of Propensity-Matched and Multivariate Analysis in Patients with Midazolam Treated

|                               | Propensity matched analysis (N=9,348) |                |                | Multivariable analysis (N=78,364) |               |                |
|-------------------------------|---------------------------------------|----------------|----------------|-----------------------------------|---------------|----------------|
|                               | Estimate                              | 95% CI         | <i>P</i> Value | Estimate                          | 95% CI        | <i>P</i> 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         |

Abbreviation: OR, odds ratio;CI,confidence interval.

## Supplementary Files

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