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ORIGINAL ARTICLE

The risk of delirium after sedation with propofol or midazolam in intensive care unit patients

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Abstract

Aim: Knowledge of risk factors may provide strategies to reduce the high burden of delirium in intensive care unit (ICU) patients. We aimed to compare the risk of delirium after deep sedation with propofol versus midazolam in ICU patients.

Methods: In this prospective cohort study, ICU patients who were in an unarousable state for ≥24 h due to continuous sedation with propofol and/or midazolam were included. Patients admitted ≤24 h, those with an acute neurological disorder and those receiving palliative sedation were excluded. ICU patients were assessed daily for delirium during the 7 days following an unarousable state due to continuous sedation.

Results: Among 950 included patients, 605 (64%) subjects were delirious during the 7 days after awaking. The proportion of subsequent delirium was higher after midazolam sedation (152/207 [73%] patients) and after both propofol and midazolam sedation (257/377 [68%] patients), compared to propofol sedation only (196/366 [54%] patients). Midazolam sedation (adjusted cause-specific hazard ratio [adj. cause-specific HR] 1.32, 95% confidence interval [CI] 1.05-1.66) and propofol and midazolam sedation (adj. cause-specific HR 1.29, 95% CI 1.06-1.56) were associated with a higher risk of subsequent delirium compared to propofol sedation only.

Conclusion: This study among sedated ICU patients suggests that, compared to propofol sedation, midazolam sedation is associated with a higher risk of subsequent delirium. This risk seems more apparent in patients with high cumulative midazolam intravenous doses. Our findings underpin the recommendations of the Society of Critical Care Medicine Pain, Agitation/sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep (disruption) guidelines to use propofol over benzodiazepines for sedation in ICU patients.

KEYWORDS
critical care, deep sedation, delirium, intensive care units

Arjen J.C. Slooter is the principal investigator of this study.

1 | INTRODUCTION

Delirium, a clinical expression of acute encephalopathy,[1] occurs frequently in intensive care unit (ICU) patients and is associated with prolonged ICU and hospital stay, and an increased risk of long-term cognitive impairment.[2–5] Knowledge of the risk factors for delirium may provide insights into strategies to reduce the high incidence and burden of delirium in ICU patients.

A systematic review pointed out several risk factors for delirium in the ICU with strong to moderate levels of evidence, such as age, mechanical ventilation and preceding coma.[6] However, inconsistent findings were found regarding the association between previous sedation with propofol and the risk of subsequent delirium.[6] Several studies indicated that benzodiazepines are a strong risk factor for delirium.[7,8] The Pain, Agitation/sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep (disruption) (PADIS) guidelines of the Society of Critical Care Medicine (SCCM) therefore suggest using non-benzodiazepine sedatives such as propofol over benzodiazepines for sedation in ICU patients, but acknowledged that the quality of evidence is low, as only one trial directly comparing propofol and midazolam is available.[8,9]

The aim of this study was to compare continuous deep sedation with propofol versus midazolam regarding the risk of subsequent delirium in ICU patients.

What is already known about this subject

- Several studies have indicated that benzodiazepines are a strong risk factor for delirium in intensive care unit (ICU) patients.
- The Pain, Agitation/sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep (disruption) guidelines of the Society of Critical Care Medicine therefore suggest using non-benzodiazepine sedatives such as propofol over benzodiazepines for sedation in ICU patients.
- However, the authors acknowledged the quality of evidence is low, as only one trial compared the risk of delirium between midazolam and propofol and found no difference.

What this study adds

- This study suggests that, compared to propofol sedation, midazolam sedation is associated with a higher risk of subsequent delirium in ICU patients.
- The risk of delirium seems more apparent in patients with high cumulative midazolam intravenous doses compared to low cumulative doses.

2 | METHODS

2.1 | Study design and study population

This single-centre, prospective cohort study on ICU delirium was conducted in a mixed medical-surgical-cardio-neuro ICU at the University Medical Center in Utrecht, the Netherlands. We included all ICU patients who were admitted between 2011-2013 and 2015-2019 for ≥24 h and who were in an unarousable state (defined as a Richmond Agitation-Sedation Scale [RASS][10] score of < −3) for ≥24 h due to continuous sedation with propofol and/or midazolam. No patients were included in 2014 due to a lack of resources regarding protocolled daily delirium assessments. Patients were excluded if they were transferred from another ICU, had an acute neurological disorder that necessitated ICU admission or had another condition that hampered detection of delirium (eg, language barrier or cognitive disability). We further excluded patients in whom no assessment of delirium was performed during ICU admission and patients who received palliative sedation. In cases of readmission during the same hospital stay, only the first admission was included.

Figure 1 illustrates the design of the time-to-event analysis. Patients were followed from the first day they were not in an unarousable state any more due to propofol and/or midazolam sedation (day 1), until the maximum follow-up time of 7 days. This criterion was established to minimize the influence of drug accumulation on the study's findings. By initiating follow-up when patients are emerging from sedation, we aimed to ensure that drug accumulation is unlikely to confound the assessment of delirium. Patients that died or were discharged from the ICU during the follow-up time were censored. If patients were sedated with propofol or midazolam multiple times, only the days after the first sedation period were included. The institutional review board waived the need for informed consent (Medical Ethics Review Committee University Medical Center Utrecht (METC UMC) Utrecht 010/056/c, 12/421/c and 19-768/c) given the non-interventional nature of the study.

2.2 | Type of sedation

Sedative selection throughout the study duration was consistently protocol-driven, aligning with the prevailing PADIS guidelines over the years.[8,11,12] Propofol was the primary choice unless contraindicated by haemodynamic instability. Midazolam was used when deep sedation was required, for example in patients with elevated intracranial pressure or difficulties in controlled mechanical ventilation. We did not employ sedation holds; instead, our approach hinged on nurse-driven sedation protocols with the objective of maintaining patients as awake, cooperative and comfortable as possible. The daily use (yes/no) and the total daily dosage of propofol and midazolam were extracted from the electronic medical records. Type of sedation during the first episode of an unarousable state due to sedation was

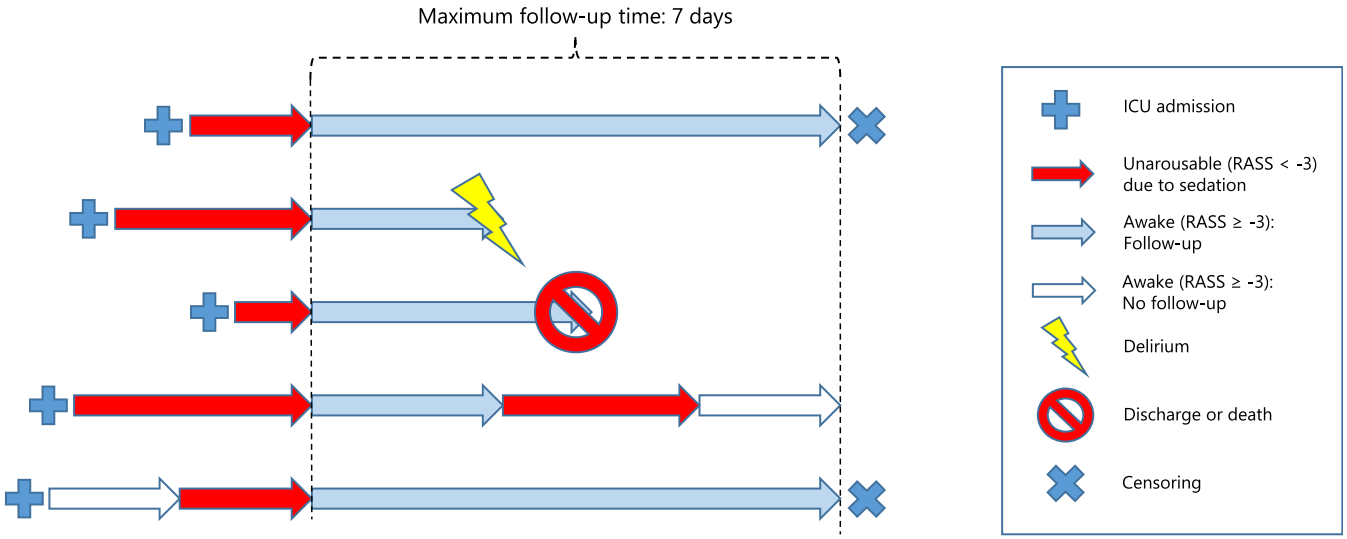

FIGURE 1 Schematic view of the time-to-event study design. Patients are followed from the day they are *not* in an unarousable state due to sedation anymore. Competing risks include discharge, death or starting sedation a second time. ICU, intensive care unit; RASS, Richmond Agitation-Sedation Scale.

used as the determinant and categorized as 'propofol only', 'midazolam only' or 'propofol and midazolam'.

We investigated two possible dose-effect relationships. First, drug-specific relationships were estimated by calculating the cumulative intravenous (IV) dose in milligrams of propofol or midazolam during the first episode of sedation for each patient. Second, the extent of sedation (regardless of sedative drug used) was estimated by calculating the Sedation Burden Index (SBI). In detail, this was done by dividing the cumulative IV dose of propofol or midazolam by the cumulative IV dose plus the minimum recommended daily dose for every day of the first sedation episode (SBI $=\sum \frac{D}{d+D}$, where D is the cumulative IV dose and d is the minimum recommended daily dose for propofol or midazolam).[12–15] The SBI was then summed over the first sedation episode, resulting in a cumulative SBI for each patient.

2.3 | Delirium assessment

As routine CAM-ICU assessments by bedside nurses lack sensitivity, the mental status of each included patient was assessed each day in the ICU using a validated five-step algorithm.[16,17] This algorithm had a sensitivity of 0.75 and specificity of 0.85 compared to a panel of delirium experts.[16] For each day, the mental state was classified as 'awake without delirium', 'delirium' or an 'unarousable state'. First, the mental status was classified as an 'unarousable state' when a patient did not reach a RASS of −3 or more in the preceding 24 h. Second, if patients had at least 1 positive Confusion Assessment Method for the ICU (CAM-ICU; performed twice daily by the bedside nurse as routine clinical practice)[18] assessment at any time in the previous 24 h, they were classified as 'delirious'. In the third step, patients were classified as 'delirious' if haloperidol or quetiapine was initiated, which is only initiated by ICU physicians as delirium treatment in our ICU. If patients were still not classified in steps 1 to 3, the RASS and CAM-ICU were applied by a trained and experienced delirium researcher in step 4. In all remaining cases (step 5), a review of the medical and nursing charts was performed.

2.4 | Additional measurements

Patient characteristics, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, type of admission, ICU length of stay and mortality were collected from electronic medical records. Furthermore, we collected the following ICU characteristics daily and used, if applicable, the maximum score during the first sedation episode per patient: mechanical ventilation status (yes/no), modified Sequential Organ Failure Assessment score (mSOFA, without the neurological component), presence of metabolic acidosis (yes/no, defined as base excess <−3 in arterial blood gas), presence of renal replacement therapy (yes/no, creatinine valuers were not collected) and use of corticosteroids, opioids, clonidine or dexmedetomidine, haloperidol, and other benzodiazepines besides intravenously administered midazolam (yes/no for each drug).

2.5 | Data analysis

Characteristics of patients were described as frequencies (%) in case of categorical data, mean (standard deviation [SD]) for normally distributed continuous data or median (first and third quartile expressed as interquartile range [IQR]) for non-normally distributed continuous data and were compared between type of sedation (propofol only, midazolam only, propofol and midazolam).

Cause-specific adjusted hazard ratios (adj. HRs) were estimated using a Cox proportional hazard model in which patients were censored if they experienced a competing risk before a delirium event. ICU discharge, ICU mortality and starting sedation a second time after the first sedation period were defined as competing risks whenever these events occurred before a delirium event. Type of sedation was included in the model in which 'midazolam only' and 'propofol and midazolam' were compared to the reference category 'propofol only'. The model was adjusted for patient characteristics (age, type of admission), the presence of delirium before the unarousable state and ICU characteristics during the days that patients were in an unarousable state due to sedation (mSOFA, mechanical ventilation [yes/no], renal replacement therapy [yes/no], metabolic acidosis [yes/no] and use of opioids [yes/no]).

Fine and Grey regression analyses were performed to model the associations between type of sedation and onset of delirium during the 7 days following an unarousable state due to propofol or midazolam sedation in a cumulative incidence plot.[19]

In a sensitivity analysis, we adjusted for the maximum level of the ICU characteristics described above during the unarousable state and the 7 days thereafter instead of the maximum level of these characteristics during the unarousable state.

To visualize the dose-effect relationships, we stratified patients within the 'propofol only' and 'midazolam only' groups based on the 10th percentiles of the cumulative IV dose into 10 categories. For the propofol only group, each category was compared to all patients in the 'midazolam only' (any cumulative dose) group and vice versa by calculating adj. HRs for onset of delirium, which were then plotted and further analysed with a two-knot linear spline regression for testing a non-linear relationship between cumulative IV dose and adj. HR. This analysis was also carried out in the entire population using the cumulative SBI.

Data cleaning as well as statistical analyses were performed in R version 4.0.3 (including 'base', 'stats', 'dplyr'[20], 'survival'[21] and 'cmprsk'[22] packages; The R Foundation for Statistical Computing, 2021).[23] A P value <0.05 (two-sides) was considered statistically significant.

3 | RESULTS

3.1 | Study population

From the 6289 patients admitted to the ICU in the study periods, 3630 patients were eligible for study inclusion (Figure 2). Of these, 950 patients were in an unarousable state for ≥24 h because of continuous deep sedation with propofol and/or midazolam. These patients had a mean age of 58 (SD 16) years, mean APACHE IV score of 70 (SD 28) and a median ICU stay of 7 (IQR 3-13) days (Table 1). Compared to sedation with propofol only (111/366 [30%]), patients receiving midazolam sedation (99/207 [48%]) or propofol and midazolam

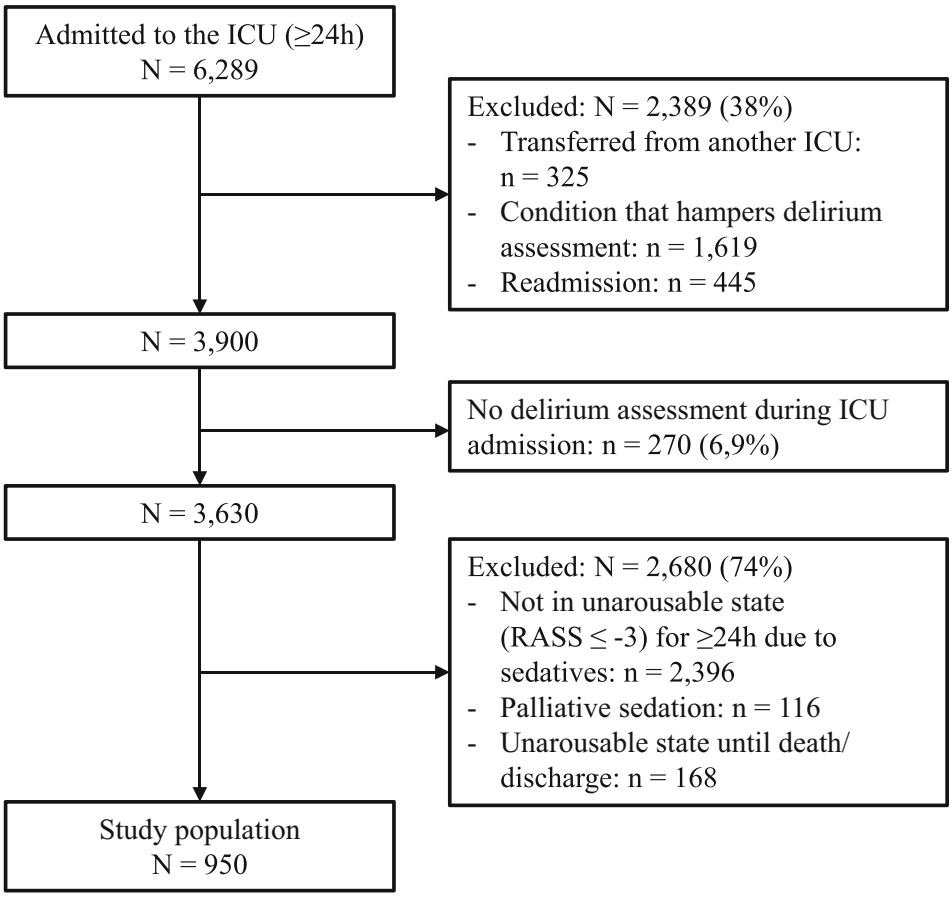

FIGURE 2 Inclusion of eligible subjects flowchart. ICU, intensive care unit; RASS, Richmond Agitation-Sedation Scale.

TABLE 1 Patient characteristics.

Patient characteristics	All patients N = 950	Propofol only N = 366	Midazolam only N = 207	Propofol and midazolam N = 377
Age in years, mean (SD)	58 (16)	59 (15)	62 (14)	54 (16)
Male sex, n (%)	635 (67%)	229 (63%)	133 (64%)	273 (72%)
Type of admission:				
Medical, n (%)	379 (40%)	111 (30%)	99 (48%)	169 (45%)
Emergency surgery, n (%)	308 (33%)	151 (41%)	42 (20%)	115 (31%)
Elective surgery, n (%)	262 (28%)	103 (28%)	66 (32%)	93 (25%)
APACHE-IV score,[a] mean (SD)	70 (28)	64 (24)	84 (29)	69 (28)
Delirium before unarousable state, n (%)	66 (7.1%)	14 (4%)	33 (16%)	19 (5%)
Maximum mSOFA score,[b] median (IQR)	8 (6-9)	8 (6-10)	9 (7-12)	8 (6-11)
SOFA circulation,[b] median (IQR)	4 (3-4)	4 (3-4)	4 (3-4)	4 (3-4)
SOFA respiration,[b] median (IQR)	3 (2-3)	2|(2-3)	3 (2-3)	3 (2-3)
Mechanical ventilation,[b] n (%)	775 (82%)	249 (68%)	182 (88%)	344 (91%)
Metabolic acidosis,[b] n (%)	671 (71%)	245 (67%)	147 (71%)	281 (75%)
Renal replacement therapy,[b] n (%)	96 (10%)	19 (5%)	38 (18%)	39 (10%)
Length of ICU stay in days, median (IQR)	7 (3-13)	5 (3-9)	9 (5-18)	9 (5-15)
ICU mortality, n (%)	26 (2.7%)	3 (1%)	12 (6%)	11 (3%)
Hospital mortality, n (%)	120 (13%)	31 (9%)	46 (22%)	43 (11%)
Cum. propofol IV dose in mg, median (IQR)	N/A	3727 (1781-6930)	N/A	4862 (1767-12 233)
Cum. midazolam IV dose in mg, median (IQR)	N/A	N/A	171 (67-398)	115 (23-370)
Length of firs sedation episode in days, median (IQR)	2 (1-3)	1 (1-2)	2 (1-4)	2 (1-3)
Cumulative SBI, median (IQR)	1.4 (0.8-2.7)	0.9 (0.8-1.7)	1.3 (0.7-2.3)	2.4 (1.2-4.2)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; Cum., cumulative; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; mSOFA, modified Sequential Organ Failure Assessment score; SD, standard deviation.
[a]Not available in 105 patients, mean reported for 845 patients. Missing APACHE IV was associated with admission type (more acute surgery), longer ICU length of stay and type of sedation (less often midazolam sedation), but was not associated with delirium.
[b]During the days that patients were in an unarousable state due to sedation.

sedation (169/377 [45%]) were more often admitted for medical reasons. They had higher APACHE IV scores (mean (SD) propofol only 64 (24), midazolam only 84 (29), propofol and midazolam 69 (28)) and were more often delirious before sedation (propofol only 14/366 (4%), midazolam only 33/207 (16%), propofol and midazolam 19/377 (5%)).

3.2 | Type of sedation and onset of delirium

Among the 950 ICU patients in an unarousable state due to propofol and/or midazolam sedation, 605 (64%) were delirious during the 7 days after awaking. The incidence of subsequent delirium was higher after midazolam sedation (152/207 [73%] patients) and after both propofol and midazolam sedation (257/377 [68%] patients), compared to propofol sedation only (196/366 [54%] patients). A total of 312 (33%) patients experienced a competing risk: 81 (26%) patients were sedated a second time after the first sedation period, 226 (72%) patients were discharged and three (1%) patients died before the end of the 7-day follow-up time and before a delirium event occurred.

The Cox proportional hazard regression analyses in which patients were censored if they experienced a competing risk

TABLE 2 Associations of propofol and midazolam sedation with subsequent delirium.

Type of sedation	Unadjusted cause-specific HR (95% CI)	Adjusted[a] cause-specific HR (95% CI)
Propofol only	Reference	
Midazolam only	1.61 (1.30-1.99)	1.32 (1.05-1.66)
Propofol and midazolam	1.38 (1.15-1.66)	1.29 (1.06-1.56)

Abbreviations: CI, confidence interval; SD, standard deviation.
[a]Adjusted for age, type of admission, delirium present before unarousable state, maximum mSOFA, mechanical ventilation, metabolic acidosis, renal replacement therapy and opioids during unarousable state.

(Table 2) showed that patients who were sedated with 'midazolam only' (adj. cause-specific HR 1.32, 95% CI 1.05-1.66) or 'propofol and midazolam' (adj. cause-specific HR 1.29, 95% CI 1.06-1.56) had a higher risk of subsequent delirium compared to sedation with propofol only. Figure 3 shows the Fine and Grey cumulative incidence plot of delirium during follow-up time compared between type of sedation.

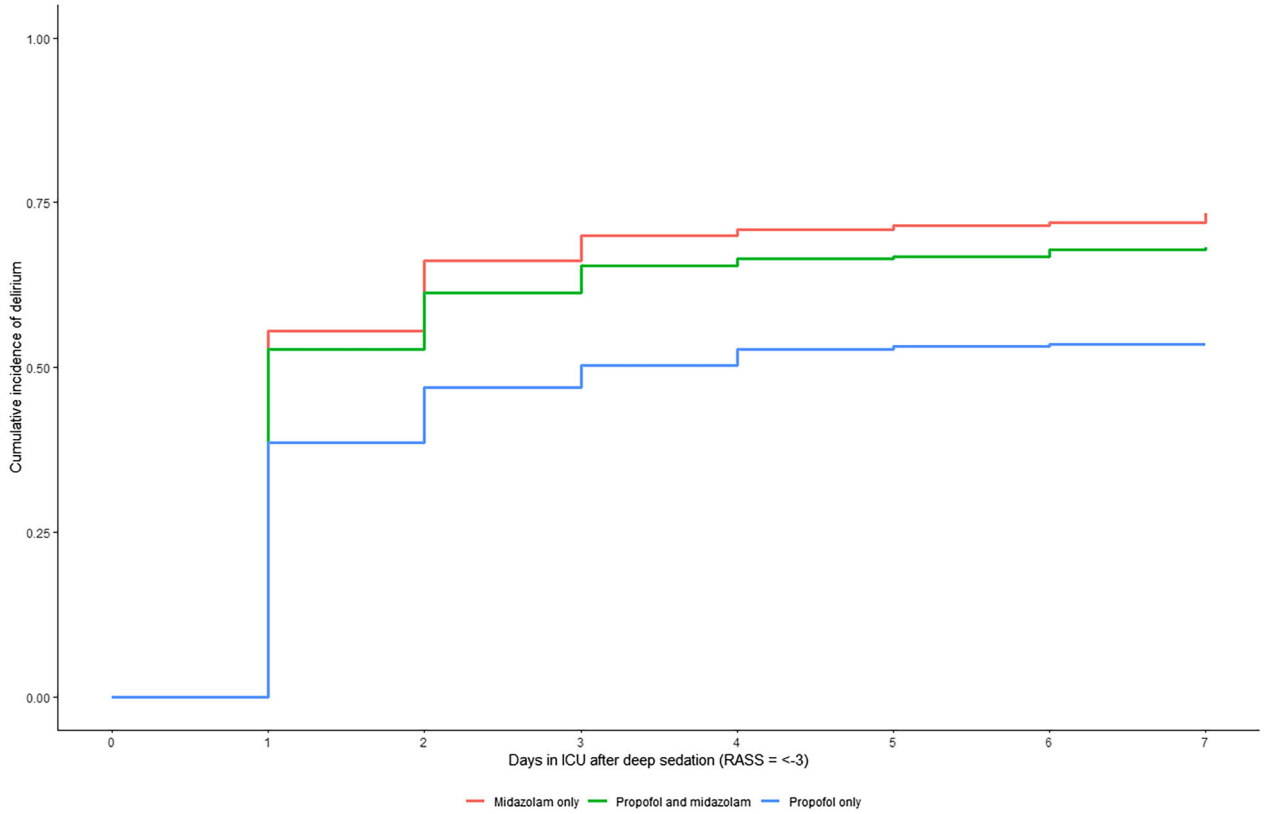

FIGURE 3 Cumulative incidence of delirium during the 7 days after an unarousable state due to sedation, compared between type of sedation used. ICU, intensive care unit; RASS, Richmond Agitation-Sedation Scale.

A sensitivity analysis in which we adjusted for the maximum level of confounders during an unarousable state and the 7 days thereafter, as opposed to the maximum level during the unarousable state, showed comparable results (see Table S1).

3.3 | Dose-effect relationship

A significant dose-effect relationship for midazolam use was found using knotted spline regression (Figure 4): compared to propofol only, a higher cumulative dose of midazolam use (≥455 mg) resulted in a stronger association with risk of delirium (adj. HR 1.67, 95% CI 1.13-2.47) as opposed to a lower cumulative midazolam dose (<455 mg; adj. HR 1.21, 95% CI 0.94-1.57, $P = 0.03$ for interaction). No apparent dose-effect relationships were found for propofol or the cumulative SBI (see Supporting Information Figures S2 and S3).

4 | DISCUSSION

We found that midazolam sedation was associated with a higher risk of subsequent delirium compared to propofol sedation.

Preceding studies comparing the risk of delirium after propofol sedation suggest that propofol may not be associated with onset of delirium but the quality of evidence was found to be low.[6,8] A prospective cohort study[24] using time-dependent analyses found that lorazepam was an independent risk factor for transitioning to delirium in ICU patients, while midazolam and non-benzodiazepine sedatives such as propofol were not associated with transitioning to delirium. Burry et al.[25] reported that benzodiazepines in the previous 48 h, but not the preceding 24 h, were associated with delirium while non-benzodiazepine sedatives including propofol were not.[25]

This study suggests that propofol is associated with a lower risk of delirium compared to midazolam. Our findings therefore underpin the recommendations of the SCCM PADIS guidelines to administer propofol over benzodiazepines for sedation in ICU patients.[8] As delirium is associated with impaired long-term outcomes,[26] it could be hypothesized that the choice of sedation has an effect on patient outcomes such as long-term cognitive impairment and mental health problems. This has not been consistently observed, but studies on this topic are limited.[7,26] Follow-up studies need to be conducted to investigate any effect of sedatives on long-term outcomes.

4.1 | Methodological considerations

The results should be interpreted in the light of some methodological considerations. A strength of our study was that a large number of patients was included, which allowed inclusion of several confounding risk factors in our models. Also, while our study was based in a single

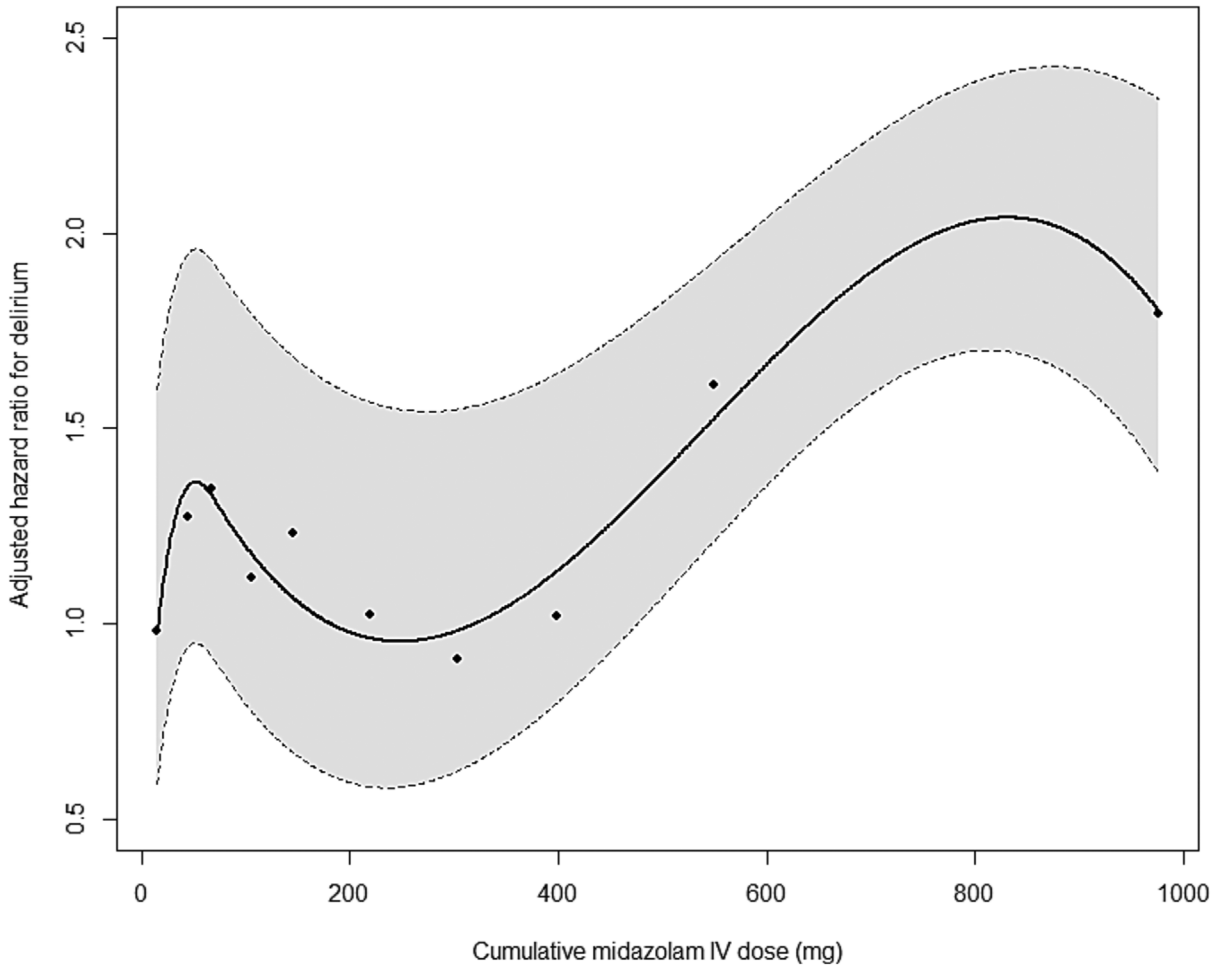

FIGURE 4 Adjusted[a] hazard ratios for onset of delirium per 10th percentile of cumulative midazolam intravenous (IV) dose versus no midazolam use, analysed with a two-knot spline regression (knots at the 25th and 75th percentiles). Dotted lines represent the same two-knot spline regressions for the upper and lower limits of the 95% confidence interval of the hazard ratios. [a]Adjusted for age, type of admission, delirium present before unarousable state, maximum mSOFA, mechanical ventilation, metabolic acidosis, renal replacement therapy and opioids during unarousable state.

ICU, the inclusion of a heterogeneous population of both medical and surgical patients enhanced its generalizability. The large sample size of 950 patients further underscores the relevance of our findings. Nonetheless, exercising caution is advised when applying these results to varied clinical settings with distinct characteristics and practices. Lastly, patients were daily assessed for the presence of delirium by a validated five-step algorithm,[16] which makes it less likely that cases were missed as the CAM-ICU performed in daily practice has known low sensitivity when compared to performance by a dedicated (research) team.[17]

However, this study has some limitations. First, as our findings are based on observational data, the choice of using a particular sedative may have depended on the patient's characteristics, which may be related to the risk of delirium as well. The patient's characteristics during the first episode of sedation (ie, mSOFA score, renal replacement therapy) indicated that patients receiving midazolam were more severely ill than patients receiving propofol. In addition, 16% of patients sedated with midazolam had already been delirious before the start of sedation compared to 4% of patients receiving propofol sedation. Although the analyses were adjusted for these characteristics, residual confounding by indication cannot be ruled out. Second, for daily measured confounders, we adjusted for the level during sedation, as this may affect the choice of sedation. Time-dependency was not taken into account. However, we performed a sensitivity analysis in which the maximum level during the unarousable state and the observation period thereafter was included in our model, and this yielded similar findings to the original model. Third, the data were collected in a single centre, which may limit the generalizability of our findings.

5 | CONCLUSION

This prospective cohort study among sedated ICU patients suggests that, compared to propofol sedation, midazolam sedation is associated with a higher risk of subsequent delirium. This risk seems more

apparent in patients with high cumulative midazolam IV doses. However, given the observational nature of our study and the limitation of being conducted in a single centre, these findings should be interpreted with caution. Despite these limitations, our findings underpin the recommendations of the SCCM PADIS guidelines to use propofol over benzodiazepines for sedation in ICU patients.

AUTHOR CONTRIBUTIONS

Thomas G. van Gelder: Formal analysis; data curation; writing—original draft. **Irene J. van Diem-Zaal:** Conceptualization; methodology; formal analysis; writing—review and editing; supervision. **Sandra M. A. Dijkstra-Kersten:** Methodology; formal analysis; writing—review and editing. **Nikki de Mul:** Writing—review and editing. **Arief Lalmohamed:** Methodology; writing—review and editing; supervision. **Arjen J. C. Slooter:** Conceptualization; resources; supervision; project administration; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data used in this study are saved in a pseudonymized form and available on request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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