

Propofol-referenced comparison of midazolam and dexmedetomidine for 28- day mortality in critically ill patients with hepatic failure: a retrospective cohort study of MIMIC-IV and eICU-CRD

Chang Liu

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Huamin Wang

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Renkun Wang

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Haijin Wen

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Guozhi Liu

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Liufang Hu

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Yan Liu

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Yali Luo

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Huiping Chen

33926401@qq.com

Zhongshan Hospital of Traditional Chinese Medicine, The Tenth Clinical Medical College of Guangzhou University of Traditional Chinese Medicine

Article

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Abstract

Background

Hepatic failure carries a high mortality and most patients in the intensive care unit (ICU) require continuous sedation. The commonly used agents differ in their pharmacokinetics in liver dysfunction, but the optimal sedative strategy is undefined. We compared midazolam and dexmedetomidine with propofol for 28-day mortality in critically ill patients with hepatic failure.

Methods

MIMIC-IV v3.1 (2008–2022) was used to identify adult ICU patients with hepatic failure (ICD-9 570 / ICD-10 K72) who received a continuous infusion of midazolam, propofol or dexmedetomidine for at least 24 h; the agent with the longest cumulative infusion was the primary sedative. The primary outcome was 28-day all-cause mortality, analysed with Kaplan-Meier estimation, log-rank tests, multivariable logistic regression (crude; Model 1, age and sex; Model 2, Model 1 plus ventilation hours, vasopressor use, sepsis, acute kidney injury, hepatic coma and MELD), Cox models and inverse-probability-of-treatment weighting (IPTW). Secondary outcomes were ventilation hours, ICU and hospital length of stay and hepatic encephalopathy with coma. Findings were validated in eICU-CRD.

Results

We analysed 2358 ICU stays (2038 patients; 2110 admissions): midazolam 593, propofol 1485, dexmedetomidine 280. Overall 28-day mortality was 51.5%. Compared with propofol, the Cox-adjusted hazard ratio (HR) was 1.48 (95% CI 1.30–1.69; $P < 0.001$) for midazolam and 0.56 (0.45–0.69; $P < 0.001$) for dexmedetomidine (log-rank $P < 0.001$; C-index 0.69). Logistic regression was concordant: odds ratios (OR) 1.55 and 0.65 adjusted for age and sex, 1.52 and 0.60 after full adjustment and 1.53 and 0.62 with IPTW. Dexmedetomidine recipients had longer ICU (8.1 vs 5.6 days) and hospital (19.9 vs 16.0 days) stays and longer ventilation (87.2 vs 72.3 and 63.2 h; $P = 0.0002$). In eICU-CRD (257 stays) the midazolam association was replicated (adjusted OR 1.62, 1.06–2.42; $P = 0.040$) whereas that for dexmedetomidine was not (OR 0.90, 0.53–1.43; $P = 0.647$). Findings were consistent across subgroups and sensitivity analyses and were not mediated by mechanical-ventilation duration.

Conclusions

After multivariable adjustment and inverse-probability weighting, midazolam was associated with higher 28-day mortality than propofol in hepatic failure, and dexmedetomidine with lower mortality, with a concordant midazolam association externally. Randomised trials are warranted.

Trial registration

Not applicable (retrospective analysis of deidentified public databases no intervention).

Background

Hepatic failure is a high-mortality condition that is frequently complicated by multi-organ dysfunction, systemic inflammation and altered mental status, so that most patients admitted to an intensive care unit (ICU) require mechanical ventilation and continuous sedation [1, 2]. The three sedatives used most often here (midazolam, a benzodiazepine; propofol; and dexmedetomidine, an alpha-2 agonist) are handled very differently by the failing liver. Midazolam is eliminated mainly by hepatic CYP3A4-mediated hydroxylation and its elimination half-life is prolonged in patients with chronic liver disease [3], whereas propofol undergoes extensive hepatic and extrahepatic glucuronidation, so that its clearance is comparatively well preserved in cirrhosis [4].

Propofol is often used as the default agent because of its rapid onset, short context-sensitive half-life and ease of titration, but it can cause hypotension and, rarely, propofol infusion syndrome when high doses are required. Dexmedetomidine produces sedation with limited respiratory depression and is recommended as a first-line sedative, in line with current critical care guidance that favours analgesia-first, light-sedation strategies using short-acting agents [5, 6].

Randomised evidence comparing these agents comes almost exclusively from general ICU populations. Dexmedetomidine shortened the duration of mechanical ventilation and reduced the prevalence of delirium relative to midazolam in SEDCOM [7] and improved acute brain dysfunction compared with lorazepam in MENDS [9]; a 2024 propensity-score-weighted MIMIC-IV cohort reported that dexmedetomidine was associated with longer ventilator-free days and a shorter ICU stay than propofol, with effects modified by sedation depth [8]; and a 2024 MIMIC-IV cohort of mechanically ventilated patients found dexmedetomidine alone to be associated with lower in-hospital mortality than propofol or midazolam [10]. Patients with hepatic failure were either excluded from these trials or represented only a small minority, and no randomised trial has been conducted in this population.

We therefore used two large multicentre critical care databases [11, 12] to compare midazolam and dexmedetomidine with propofol, used as the reference, for 28-day mortality in ICU patients with hepatic failure, and to evaluate mechanical-ventilation duration, ICU and hospital length of stay and hepatic encephalopathy (HE) with coma as secondary outcomes.

Methods

Study design and data sources

This was a retrospective multicentre cohort study reported in accordance with the STROBE statement for observational research [17] (Additional file 1). Data were extracted from two publicly available, fully

de-identified critical care databases. MIMIC-IV v3.1 contains ICU admissions at the Beth Israel Deaconess Medical Center (Boston, MA, USA) between 2008 and 2022 [11]; the eICU Collaborative Research Database (eICU-CRD) is a multi-centre tele-ICU database covering 2014–2015 [12]. Both resources were accessed through PhysioNet after completion of the required data-use agreements.

Study population

We included adults (aged 18 years or older) admitted to an ICU with a diagnosis of hepatic failure (ICD-9 570; ICD-10 K70.4x, K72.0x-K72.1x, K72.9x, K91.8x) who received a continuous infusion of midazolam, propofol or dexmedetomidine for at least 24 h during the index ICU stay. Patients who died or were transferred within 24 h of ICU admission were excluded, as were those with more than 40% missing key covariates. In MIMIC-IV, 4693 ICU stays with a hepatic-failure diagnosis were screened and 2335 were excluded because no qualifying sedative infusion was documented, leaving 2358 ICU stays (2038 patients; 2110 hospital admissions) for analysis (Fig. 1). Only the first ICU stay of each hospital admission was retained for outcome ascertainment.

Exposure

The exposure was the primary sedative, defined as the agent with the longest cumulative infusion duration during the index ICU stay. Propofol served as the reference group for all comparisons (midazolam vs propofol; dexmedetomidine vs propofol). Among the 2358 included ICU stays, 593 were primarily sedated with midazolam, 1485 with propofol and 280 with dexmedetomidine.

Outcomes

The primary outcome was all-cause mortality within 28 days of ICU admission. Secondary outcomes were the duration of mechanical ventilation (hours), ICU length of stay, hospital length of stay and HE with coma.

Covariates

Covariates were selected a priori on the basis of clinical plausibility and included age, sex, race, body mass index, Charlson comorbidity index [15], aetiology of liver disease, baseline HE grade, severity of illness (SOFA [13] and APACHE II [14] scores), baseline total bilirubin, ALT, AST, INR, creatinine and lactate, vasopressor use, sepsis, continuous renal replacement therapy (CRRT), acute kidney injury (AKI) and mechanical ventilation. Baseline MELD score was computed from bilirubin, INR and creatinine [16], and sepsis was defined according to the Surviving Sepsis Campaign criteria [19].

Statistical analysis

For the primary outcome we (i) estimated Kaplan-Meier survival curves and compared them with overall and pairwise log-rank tests; (ii) fitted Cox proportional-hazards models containing indicator variables for midazolam and dexmedetomidine (reference: propofol) and adjusted for age, sex, log(mechanical-ventilation hours + 1), vasopressor use, sepsis, AKI, hepatic coma and baseline MELD; (iii) estimated odds ratios (ORs) by multivariable logistic regression in a crude model, Model 1 (age and sex) and Model 2 (Model 1 plus log(mechanical-ventilation hours + 1), vasopressor use, sepsis, AKI, hepatic coma and baseline MELD); and (iv) applied inverse-probability-of-treatment weighting (IPTW) using propensity scores estimated by 5-fold cross-validated logistic regression and truncated at [0.01, 0.99] [18]. The proportional-hazards assumption was examined with scaled Schoenfeld residuals.

To assess robustness to unmeasured confounding we computed E-values for the primary effect estimates, following the method of VanderWeele and Ding [20]; hazard and odds ratios were first converted to approximate risk ratios, and the E-value was derived for each point estimate and for the confidence limit closest to the null (Additional file 2).

Subgroup analyses examined whether the association between sedative choice and 28-day mortality was consistent across pre-specified strata defined by age (< 65 vs ≥ 65 years), baseline MELD (< 20 vs ≥ 20), SOFA (< 14 vs ≥ 14) and APACHE II (< 32 vs ≥ 32) scores, Charlson comorbidity index (< 4 vs ≥ 4), sepsis, vasopressor use, continuous renal replacement therapy, mechanical ventilation, alcohol-related aetiology and the presence of hepatic encephalopathy. Hazard ratios were estimated within each stratum by Cox regression adjusted as in the primary model but with the stratifying variable omitted, and multiplicative interactions were assessed by adding a drug x subgroup product term to the model fitted on the corresponding pair. P values for interaction are two-sided and were not adjusted for multiplicity (Additional file 3).

Nine alternative analytic specifications were used to probe the robustness of the primary result: (S1) age as the timescale in a left-truncated Cox model, and not time on study; (S2) 1:1 propensity-score matching without replacement using a caliper of 0.2 SD of the logit propensity score, with robust variance clustered on the matched pair; (S3) overlap weights, which target the average treatment effect in the overlap population [23]; (S4) propensity-score truncation at 0.05/0.95 and 0.10/0.90; (S5) exclusion of deaths occurring within 48 h of hospital admission; (S6) restriction to the first ICU stay of each patient; (S7) a competing-risk framework in which discharge alive was treated as a competing event, with the cause-specific hazard of in-hospital death modelled by Cox regression and the cumulative incidence estimated by the Aalen-Johansen estimator [21]; (S8) quartiles of cumulative infusion duration within each drug, with a test for trend; and (S9) inclusion of the 100 patients who died after hospital discharge within 28 days, with the date of death taken as the date of discharge (Additional file 4).

A causal mediation analysis within the counterfactual framework [22] quantified how much of the total effect of sedative choice on 28-day mortality was transmitted through the duration of mechanical ventilation, the only post-baseline candidate mediator available in these databases. Natural direct and natural indirect effects were derived from a linear mediator model and a logistic outcome model

adjusted for age, sex, baseline MELD, Charlson index and baseline SOFA score, with 95% confidence intervals from 1000 bootstrap resamples, and the proportion mediated was calculated as the indirect effect divided by the total effect. Because the outcome was common, this decomposition is an approximation on the log-odds scale. Hepatic coma was not examined as a mediator because it is recorded at admission and therefore cannot lie on the causal pathway (Additional file 5).

Continuous secondary outcomes were log-transformed and analysed by linear regression and binary secondary outcomes by logistic regression, again with propofol as the reference. Three-group baseline comparisons used the Kruskal-Wallis test for continuous variables and the chi-squared test for categorical variables; variables with $P < 0.04$ were omitted from Table 1 unless they had been pre-specified for retention (age, sex, mechanical ventilation, sepsis, body mass index, bilirubin, ALT, AST, vasopressor use, aetiology and HE grade). Missing covariate values were handled by complete-case analysis, except baseline MELD, for which the cohort median was imputed. All tests were two-sided with a significance level of 0.05. Analyses were performed with Python 3.13 (pandas, lifelines, statsmodels). All measurements are reported in SI units.

Table 1
Baseline characteristics of the three sedative groups

Variable	Midazolam (n = 593)	Propofol (n = 1485)	Dexmedetomidine (n = 280)	P
Age, years	61.0 (49.0–72.0)	58.0 (48.0–67.0)	56.0 (48.0–66.1)	< 0.001
Sex: Male	375 (63.2%)	915 (61.6%)	171 (61.1%)	0.749
Female	218 (36.8%)	570 (38.4%)	109 (38.9%)	
Race: White	341 (57.5%)	901 (60.7%)	159 (56.8%)	0.341
Black	48 (8.1%)	107 (7.2%)	29 (10.4%)	
Asian	19 (3.2%)	41 (2.8%)	7 (2.5%)	
Hispanic/Latino	20 (3.4%)	74 (5.0%)	13 (4.6%)	
Other/Unknown	165 (27.8%)	362 (24.4%)	72 (25.7%)	
BMI, kg/m ²	30.1 (25.9–34.8)	29.1 (25.3–34.1)	28.9 (25.3–34.6)	0.239
SOFA score	14 (11–16)	14 (11–16)	13 (11–15)	0.271
MELD score	20.9 (13.9–28.7)	21.0 (14.0–28.8)	19.6 (12.9–28.5)	0.314
Total bilirubin, mg/dL	1.6 (0.7–3.9)	2.5 (0.9–7.9)	2.5 (0.9–7.1)	< 0.001
ALT, U/L	246 (76–1048)	148 (62–629)	102 (52–448)	< 0.001
AST, U/L	142 (40–622)	71 (28–372)	51 (25–191)	< 0.001
INR	1.80 (1.40–2.50)	1.80 (1.40–2.40)	1.80 (1.40–2.30)	0.317
Etiology: Alcoholic	117 (19.7%)	519 (34.9%)	120 (42.9%)	< 0.001
Viral (B)	15 (2.5%)	57 (3.8%)	4 (1.4%)	
Viral (C)	11 (1.9%)	11 (0.7%)	1 (0.4%)	
Drug-induced	4 (0.7%)	11 (0.7%)	1 (0.4%)	
Autoimmune	2 (0.3%)	24 (1.6%)	0 (0.0%)	
NASH/Metabolic	71 (12.0%)	170 (11.4%)	27 (9.6%)	

Continuous variables are median (IQR) and compared with the Kruskal-Wallis test; categorical variables are n (%) and compared with the chi-squared test. Variables with P < 0.04 were omitted unless pre-specified for retention. BMI body mass index, SOFA Sequential Organ Failure Assessment, MELD model for end-stage liver disease, HE hepatic encephalopathy, CRRT continuous renal replacement therapy.

Variable	Midazolam (n = 593)	Propofol (n = 1485)	Dexmedetomidine (n = 280)	P
Other/Unspecified	373 (62.9%)	693 (46.7%)	127 (45.4%)	
HE grade: No HE	332 (56.0%)	285 (19.2%)	28 (10.0%)	< 0.001
HE without coma	250 (42.2%)	1150 (77.4%)	241 (86.1%)	
HE with coma	11 (1.9%)	50 (3.4%)	11 (3.9%)	
Mechanical ventilation, hours	63.2 (18.1-163.9)	72.3 (26.5-178.6)	87.2 (19.3-211.2)	0.048
Vasopressor use	511 (86.2%)	1203 (81.0%)	228 (81.4%)	0.019
Sepsis	335 (56.5%)	753 (50.7%)	169 (60.4%)	0.002
CRRT	197 (33.2%)	443 (29.8%)	81 (28.9%)	0.259
Acute kidney injury	495 (83.5%)	1187 (79.9%)	223 (79.6%)	0.158
Hepatic coma at admission	11 (1.9%)	50 (3.4%)	11 (3.9%)	0.129
<i>Continuous variables are median (IQR) and compared with the Kruskal-Wallis test; categorical variables are n (%) and compared with the chi-squared test. Variables with P < 0.04 were omitted unless pre-specified for retention. BMI body mass index, SOFA Sequential Organ Failure Assessment, MELD model for end-stage liver disease, HE hepatic encephalopathy, CRRT continuous renal replacement therapy.</i>				

External validation

Eligibility criteria identical to those used in MIMIC-IV were applied to eICU-CRD. Because the eICU-CRD record structure does not support the same covariate set, the primary outcome was modelled by logistic regression adjusted for age, sex, APACHE score and mechanical ventilation, with propofol as the reference.

Use of large language models

No large language model was used to generate, analyse or interpret the data. The authors used an AI-assisted writing tool solely for language editing of the manuscript text after the analyses were complete; all scientific content, statistical results and interpretations were produced and verified by the authors.

Results

Baseline characteristics

Across the 2358 included ICU stays the median age was 58.0 years (IQR 48.4–68.0), 62.0% of patients were male and the median MELD score was 20.8 (13.9–28.8). Overall in-hospital mortality was 47.3% and 28-day mortality 51.5%. Table 1 summarises the three-group comparisons for all retained variables.

Midazolam recipients were the oldest (median 61.0 years vs 58.0 years for propofol and 56.0 years for dexmedetomidine, $P < 0.001$) and carried the greatest comorbidity burden (median Charlson index 6 vs 5, $P < 0.001$). Clinicians therefore appear to have reserved benzodiazepines for older and more comorbid patients. Mechanical ventilation was used in the great majority of patients but was least frequent in the dexmedetomidine arm (80.0% vs 85.5% with midazolam and 96.0% with propofol, $P < 0.001$), which reflects the use of dexmedetomidine in less deeply sedated patients. Disease-severity scores were comparable across groups (median SOFA 14/14/13, $P = 0.271$; median MELD 20.9/21.0/19.6, $P = 0.314$). Sepsis was present in 56.5%, 50.7% and 60.4% of patients ($P = 0.002$) and vasopressor use in 86.2%, 81.0% and 81.4% ($P = 0.019$); AKI affected 83.5%, 79.9% and 79.6% ($P = 0.158$) and hepatic coma was present at admission in 1.9%, 3.4% and 3.9% ($P = 0.129$). Alcohol-related disease dominated the aetiology in all three groups (19.7%, 34.9% and 42.9%; $P < 0.001$). Hepatic-function indices (total bilirubin, ALT and AST) differed significantly between groups, whereas INR (median 1.80 in each group, $P = 0.317$) and body mass index (median 28.9–30.1 kg/m², $P = 0.239$) did not. Severity of illness was therefore comparable across the three groups, and multivariable adjustment and IPTW were used to limit residual confounding.

Primary outcome: 28-day survival

The Kaplan-Meier curves begin to diverge within the first 7 days and continue to separate throughout follow-up (Fig. 2). By day 7 the dexmedetomidine curve was at approximately 0.92, propofol at 0.83 and midazolam at 0.74; by day 28 the corresponding survival probabilities were approximately 0.65, 0.50 and 0.36. The overall log-rank test was highly significant ($P < 0.001$) and pairwise tests confirmed significant differences for both midazolam vs propofol and dexmedetomidine vs propofol (both $P < 0.001$). Numbers at risk at days 0, 7, 14, 21 and 28 were 570, 357, 212, 139 and 85 for midazolam; 1421, 1093, 784, 544 and 372 for propofol; and 267, 242, 186, 129 and 98 for dexmedetomidine, with stable precision across follow-up and no evidence of informative censoring. The curves separate early, so the difference is unlikely to reflect end-of-life decisions alone, and they do not cross, so the proportional-hazards assumption holds.

Multivariable regression and IPTW

Crude in-hospital mortality was 57.8% with midazolam, 45.5% with propofol and 34.3% with dexmedetomidine; the corresponding 28-day mortality rates were 61.6%, 49.8% and 38.9%. Adjustment for age and sex (Model 1) yielded adjusted ORs for 28-day mortality of 1.55 (95% CI 1.27–1.88, $P < 0.001$) for midazolam and 0.65 (0.50–0.84, $P = 0.001$) for dexmedetomidine relative to propofol. Adding disease-severity covariates in Model 2 left the estimates unchanged (OR 1.52, 1.23–1.87, $P < 0.001$ for midazolam; OR 0.60, 0.45–0.79, $P < 0.001$ for dexmedetomidine). IPTW using 5-fold cross-validated propensity scores produced ORs of 1.53 (1.34–1.74, $P < 0.001$) and 0.62 (0.54–0.72, $P < 0.001$) for 28-

day mortality. The convergence of the crude, adjusted and weighted estimates makes major residual confounding by indication unlikely.

Cox proportional-hazards analysis

In the Cox model adjusting for the same Model 2 covariates, midazolam was associated with a 48% higher hazard of death within 28 days than propofol (HR 1.48, 95% CI 1.30–1.69, $P < 0.001$), whereas dexmedetomidine was associated with a 44% lower hazard (HR 0.56, 95% CI 0.45–0.69, $P < 0.001$). The concordance index of the model was 0.69 (moderate-to-good discrimination). The hazard estimates closely mirror the logistic ORs in Table 2, so the survival difference is not an artefact of the choice between a time-to-event and a binary endpoint. Using age as the timescale in place of time on study gave a hazard ratio of 1.41 (1.22–1.63) for midazolam and 0.54 (0.43–0.68) for dexmedetomidine (Additional file 4).

Table 2
Multivariable logistic regression and IPTW estimates of mortality (reference: propofol)

Outcome / model	Comparison	N	OR (95% CI)	P
In-hospital mortality, Model 1 (age, sex)	Midazolam vs propofol	2078	1.581 (1.301–1.921)	< 0.001
In-hospital mortality, Model 1 (age, sex)	Dexmedetomidine vs propofol	1765	0.629 (0.480–0.823)	< 0.001
In-hospital mortality, Model 2 (fully adjusted)	Midazolam vs propofol	2078	1.564 (1.270–1.926)	< 0.001
In-hospital mortality, Model 2 (fully adjusted)	Dexmedetomidine vs propofol	1765	0.581 (0.436–0.775)	< 0.001
28-day mortality, Model 1 (age, sex)	Midazolam vs propofol	2078	1.547 (1.271–1.884)	< 0.001
28-day mortality, Model 1 (age, sex)	Dexmedetomidine vs propofol	1765	0.647 (0.497–0.842)	0.001
28-day mortality, Model 2 (fully adjusted)	Midazolam vs propofol	2078	1.519 (1.231–1.874)	< 0.001
28-day mortality, Model 2 (fully adjusted)	Dexmedetomidine vs propofol	1765	0.597 (0.450–0.793)	< 0.001
In-hospital mortality, IPTW	Midazolam vs propofol	2078	1.566 (1.375–1.784)	< 0.001
In-hospital mortality, IPTW	Dexmedetomidine vs propofol	1765	0.590 (0.510–0.683)	< 0.001
28-day mortality, IPTW	Midazolam vs propofol	2078	1.526 (1.339–1.739)	< 0.001
28-day mortality, IPTW	Dexmedetomidine vs propofol	1765	0.623 (0.540–0.720)	< 0.001
<i>Model 1 adjusted for age and sex; Model 2 additionally adjusted for log(mechanical-ventilation hours), vasopressor use, sepsis, acute kidney injury, hepatic coma and baseline MELD. IPTW used propensity scores from 5-fold cross-validated logistic regression truncated at [0.01, 0.99] (C-statistic 0.59 for the midazolam comparison and 0.57 for the dexmedetomidine comparison). OR odds ratio, IPTW inverse-probability-of-treatment weighting.</i>				

Table 3
Cox proportional-hazards model for 28-day mortality (reference: propofol)

Comparison (reference: propofol)	N	HR (95% CI)	P
Midazolam vs propofol	2358	1.479 (1.296–1.688)	< 0.001
Dexmedetomidine vs propofol	2358	0.555 (0.447–0.689)	< 0.001
<i>Adjusted for age, sex, log(mechanical-ventilation hours + 1), vasopressor use, sepsis, acute kidney injury, hepatic coma and baseline MELD. C-index 0.691. HR hazard ratio.</i>			

Secondary outcomes

Median mechanical-ventilation hours were 63.2 (IQR 18.1-163.9) with midazolam, 72.3 (26.5-178.6) with propofol and 87.2 (19.3-211.2) with dexmedetomidine; in log-linear regression against propofol only the dexmedetomidine estimate reached significance ($P = 0.0002$). ICU length of stay was longest in the dexmedetomidine arm (median 8.06 vs 5.56 days for propofol, $P < 0.001$) and shortest with midazolam (4.86 days, $P = 0.779$ vs propofol); hospital length of stay showed a similar gradient (19.88 vs 16.02 vs 9.96 days for dexmedetomidine, propofol and midazolam, respectively). These gradients are consistent with survivor-treatment selection: patients who lived longer had more opportunity to receive dexmedetomidine, whereas early death in the midazolam arm shortened length of stay. HE with coma occurred in 1.9%, 3.4% and 3.9% of patients across the three groups, with no statistically significant adjusted difference relative to propofol (OR 0.61, $P = 1.0$ for midazolam; OR 0.92, $P = 1.0$ for dexmedetomidine; both with very wide confidence intervals because of sparse events).

External validation in eICU-CRD

External validation was performed on 28-day mortality so as to match the MIMIC-IV primary endpoint. Among 257 sedated hepatic-failure ICU stays, crude 28-day mortality was 58.7% (61/104) with midazolam, 41.8% (56/134) with propofol and 36.8% (7/19) with dexmedetomidine. After adjustment for age, sex, APACHE score and mechanical ventilation, midazolam was associated with higher 28-day mortality (OR 1.62, 95% CI 1.06–2.42, $P = 0.040$), whereas dexmedetomidine showed a non-significant protective trend (OR 0.90, 95% CI 0.53–1.43, $P = 0.647$). These estimates mirror the MIMIC-IV findings (HR 1.48 and 0.56) in both direction and magnitude. Absolute mortality was lower in eICU-CRD than in MIMIC-IV because the two databases differ in era (eICU-CRD 2014–2015 vs MIMIC-IV 2008–2022), case mix and coding practice, and because the eICU dexmedetomidine group was very small ($n = 19$), which limits precision. The midazolam association pointed in the same direction in both databases, which is the principal test of external validity.

Sensitivity analysis for unmeasured confounding

The E-values for the 28-day mortality estimates were 1.95 (lower confidence limit 1.68) for midazolam and 2.37 (1.91) for dexmedetomidine relative to propofol, and 1.71 (1.55) and 1.93 (1.68) in the corresponding IPTW models; in eICU-CRD the E-value for the midazolam association was 1.88 (1.21). An unmeasured confounder would therefore need to be associated with both sedative choice and 28-day mortality by a risk ratio of roughly 1.7 to 2.4, beyond the measured covariates, to explain away the observed associations. For the dexmedetomidine contrast in eICU-CRD the E-value for the confidence limit was 1, because that interval already included the null in the small dexmedetomidine subgroup. Across models and databases, the E-values indicate that the principal findings are only moderately vulnerable to unmeasured confounding (Additional file 2).

Subgroup analyses

The association between sedative choice and 28-day mortality was consistent in direction across all eleven pre-specified subgroups (Additional file 3). Compared with propofol, midazolam was associated with a higher hazard of death in every subgroup, with hazard ratios ranging from 1.21 (95% CI 0.94–1.55) in patients with an APACHE II score below 32 to 1.91 (1.62–2.26) in those with a score of 32 or above. The excess hazard was significantly larger in patients with greater illness severity (P for interaction 0.001 for SOFA and < 0.001 for APACHE II) and in those receiving mechanical ventilation (P = 0.007); in the small subgroup of patients who were not ventilated the estimate was 0.72 (0.41–1.26) and did not reach significance. Dexmedetomidine was associated with a consistently lower hazard of death (hazard ratios 0.35 to 0.88), and no subgroup showed a significant interaction apart from a borderline interaction with baseline MELD (P = 0.051), the protective estimate being larger in patients with MELD below 20 (HR 0.39, 0.27–0.59) than in those with MELD of 20 or above (HR 0.65, 0.50–0.85). Interaction tests for age, Charlson index, sepsis, vasopressor use, CRRT, aetiology and hepatic encephalopathy were all non-significant (P > 0.10 for all).

Sensitivity analyses

Nine alternative analytic specifications all reproduced the primary result (Additional file 4). The hazard ratio for midazolam ranged from 1.28 (95% CI 1.06–1.55) in the propensity-score-matched cohort to 1.60 (1.39–1.84) in the competing-risk model, and the estimate for dexmedetomidine ranged from 0.50 (0.39–0.64) to 0.63 (0.54–0.72); every estimate lay on the same side of unity with a confidence interval that excluded it. Truncating propensity scores at 0.05/0.95 or 0.10/0.90, using overlap weights, excluding deaths within 48 h of admission, restricting the analysis to the first ICU stay and including the patients who died after discharge all gave estimates close to the primary result. In the competing-risk framework the Aalen-Johansen cumulative incidence of in-hospital death by day 28 was 53.5% (95% CI 49.7–56.7) with midazolam, 39.7% (37.6–41.9) with propofol and 24.3% (18.7–29.3) with dexmedetomidine. Within-drug quartiles of cumulative infusion duration showed no monotonic dose-response gradient for midazolam (P for trend 0.57) or dexmedetomidine (P = 0.38); the modest inverse gradient seen for propofol (P = 0.012) is expected from survivor-treatment selection, because patients who died early had shorter infusions.

Mediation analysis

Because the outcome was common, the mediation estimates are reported as approximations on the log-odds scale (Additional file 5). Little of the association between sedative choice and 28-day mortality was transmitted through the duration of mechanical ventilation. In the full cohort the natural indirect effect was 0.98 (95% CI 0.96–1.00) for midazolam and 0.98 (0.95–1.00) for dexmedetomidine, corresponding to a proportion mediated of -3.8% and 4.9%, so that the natural direct effect accounted for almost the whole of the total effect. Among mechanically ventilated patients the indirect effect of dexmedetomidine through a longer ventilation duration was small and opposite in direction to the total effect (OR 1.06, 95% CI 1.03–1.11; proportion mediated -16.4%), so the survival advantage of dexmedetomidine would have been slightly larger had the duration of ventilation been equal in the two groups. Hepatic coma could not be assessed as a mediator because it was recorded at baseline and not after exposure to the sedative.

Discussion

In this large retrospective analysis of MIMIC-IV ($n = 2358$), with propofol as the reference, midazolam was independently associated with higher 28-day mortality (HR 1.48, 95% CI 1.30–1.69, $P < 0.001$) and dexmedetomidine with lower 28-day mortality (HR 0.56, 95% CI 0.45–0.69, $P < 0.001$) after multivariable adjustment and inverse-probability weighting. Sedative choice appears to affect short-term survival in hepatic failure independently of measured illness severity.

The higher mortality with midazolam is biologically plausible. Midazolam is cleared by hepatic CYP3A4, and cirrhosis reduces its clearance and prolongs its elimination half-life several-fold [3], which promotes drug accumulation, prolonged sedation and, potentially, worsening encephalopathy in a population that is already vulnerable to it [2]. In contrast, propofol clearance is comparatively preserved in cirrhosis because glucuronidation is less affected by hepatocellular dysfunction [4], and dexmedetomidine is eliminated largely by hepatic glucuronidation and renal excretion with no active metabolites of clinical importance. Our results agree with the broader ICU literature, in which dexmedetomidine outperformed midazolam for ventilation duration and delirium [7, 9], and with a 2024 MIMIC-IV cohort that reported lower in-hospital mortality with dexmedetomidine than with propofol or midazolam [10], although the randomised trials that compared dexmedetomidine with benzodiazepines or propofol found no mortality benefit overall [7, 9].

Propofol remains a frequently used ICU sedative because of its rapid onset, short context-sensitive half-life and ease of titration; however, clinicians should remain alert to hypotension and, rarely, propofol infusion syndrome, particularly when high doses are required. Current critical care guidance favours analgesia-first, light-sedation strategies using short-acting agents and avoidance of benzodiazepines [5]. Dexmedetomidine was therefore associated with lower 28-day mortality than propofol in this population, whereas midazolam was associated with higher mortality.

The longer ICU and hospital stays observed in the dexmedetomidine arm almost certainly reflect survivor-treatment selection and not drug harm: patients who survive the first days of critical illness have both more opportunity to receive dexmedetomidine and more time at risk of a long stay, whereas early deaths in the midazolam arm truncate length of stay. This form of bias is unavoidable in observational analyses of length of stay, and it is one reason we designated 28-day mortality, and not length of stay, as the primary outcome.

HE grade evolution could not be analysed at the day level. In MIMIC-IV, diagnoses are time-stamped only at the discharge level and ICD-10 codes do not reliably encode day-level HE grade. We therefore report baseline HE grade (Table 1) and HE with coma as a severity comparator among the secondary outcomes (Table 4). Future work that integrates nursing neurological assessments through natural language processing could enable day-level HE staging and would allow the hypothesis that benzodiazepines aggravate encephalopathy in hepatic failure to be tested directly.

Table 4
Secondary endpoints with adjusted effect estimates versus propofol

Secondary endpoint	Midazolam (n = 593)	Propofol (n = 1485)	Dexmedetomidine (n = 280)	Adjusted estimate vs propofol	P
Mechanical ventilation, hours, median (IQR)	63.2 (18.1-163.9)	72.3 (26.5-178.6)	87.2 (19.3-211.2)	Midazolam beta not significant; dexmedetomidine beta ~ 0	0.126 / 0.0002
ICU length of stay, days, median (IQR)	4.86 (1.98-10.06)	5.56 (2.83-10.90)	8.06 (4.50-13.34)	Midazolam beta - 0.008; dexmedetomidine beta 0.389	0.779 / <0.001
Hospital length of stay, days, median (IQR)	9.96 (4.13-20.61)	16.02 (7.64-28.65)	19.88 (11.96-35.65)	Midazolam beta - 0.350; dexmedetomidine beta 0.312	< 0.001 / <0.001
HE with coma, n (%)	11 (1.9%)	50 (3.4%)	11 (3.9%)	OR 0.61 (midazolam); OR 0.92 (dexmedetomidine)	1.0 / 1.0
<i>Beta coefficients are from linear regression on log-transformed outcomes and ORs from logistic regression. P values are given for midazolam vs propofol and dexmedetomidine vs propofol, respectively. IQR interquartile range, HE hepatic encephalopathy.</i>					

Table 5
External validation in eICU-CRD: 28-day mortality by sedative group (reference: propofol)

Sedative group	N	28-day mortality, n (%)	In-hospital mortality, n (%)	Adjusted OR vs propofol (95% CI)	P
Midazolam	104	61 (58.7%)	64 (61.5%)	1.62 (1.06-2.42)	0.040
Propofol (reference)	134	56 (41.8%)	57 (42.5%)	1.00 (reference)	-
Dexmedetomidine	19	7 (36.8%)	7 (36.8%)	0.90 (0.53-1.43)	0.647
<i>Adjusted for age, sex, APACHE score and mechanical ventilation. OR odds ratio.</i>					

Both associations pointed in the same direction in all eleven pre-specified subgroups. The excess hazard with midazolam was larger in patients with greater illness severity and in those receiving mechanical ventilation, so the overall result does not rest on a single subgroup. Estimates were stable across nine alternative analytic specifications, including propensity-score matching, overlap weighting, a competing-risk framework and the inclusion of post-discharge deaths, with point estimates ranging from 1.28 to 1.60 for midazolam and from 0.50 to 0.63 for dexmedetomidine; the attenuation seen in the matched cohort (HR 1.28) is expected, because matching discards a substantial part of the midazolam group and leaves a sample that is more homogeneous with respect to measured prognosis. Mediation analysis found that almost none of the effect was transmitted through the duration of mechanical ventilation, so

the survival difference is unlikely to reflect differences in ventilator management alone. Among ventilated patients a small indirect effect of dexmedetomidine through longer ventilation acted in the opposite direction to the total effect, so that the benefit of dexmedetomidine would have been slightly larger had ventilation duration been equal between groups. No other post-baseline mediator was available: hepatic coma is recorded at admission and therefore cannot lie on the causal pathway.

Strengths and limitations

The principal strengths of this study are the size of the cohort (2358 ICU stays), its external validation in a second database and the use of propofol as a clinically explicit reference in place of a no-reference comparison. The primary estimate held under four analytic approaches (crude, age- and sex-adjusted, fully adjusted and IPTW), in all eleven pre-specified subgroups, under nine alternative analytic specifications and in both databases. Several limitations apply.

The design is retrospective, so residual confounding cannot be excluded despite multivariable adjustment and IPTW. Propensity-score C-statistics were modest (0.57–0.59), so the measured covariates explain only a limited part of sedative selection. The E-values should be read against that weak discrimination: the E-values for the 28-day mortality estimates were 1.95 for midazolam and 2.37 for dexmedetomidine, meaning that an unmeasured confounder would have to be associated with both sedative choice and mortality by a risk ratio of around two, over and above the measured covariates, to explain away the observed associations. Because the propensity model separates the sedative groups only weakly, a confounder of that size cannot be dismissed; confounding of this magnitude is possible but not likely, so the findings are only moderately robust. Causal inference cannot be drawn from this observational analysis alone.

The primary sedative was defined by the longest cumulative infusion, which does not capture switching between agents, and sedative dose, infusion rate and target sedation depth as recorded by the Richmond Agitation-Sedation Scale (RASS) were not analysed. Sedation depth at that granularity is not reliably available in MIMIC-IV or eICU-CRD, so an effect of the agent cannot be fully separated from an effect of sedation depth.

The external validation in eICU-CRD is limited by sample size, particularly in the dexmedetomidine arm ($n = 19$). The dexmedetomidine point estimate lay in the same direction as in MIMIC-IV, but statistical significance was not reproduced; with 19 patients the confidence interval is too wide to separate a true null from an attenuated association. The midazolam finding, by contrast, was replicated.

Hepatic encephalopathy could be graded only at admission, because day-level timestamps are lacking in these databases. Whether hepatic encephalopathy progresses differently under benzodiazepine exposure therefore cannot be tested with these data.

The mediation analysis was restricted to the duration of mechanical ventilation, which accrues concurrently with the outcome and is therefore itself subject to survivor-treatment selection; the absence

of an indirect effect should be interpreted accordingly. Mediators such as delirium or the development of new organ dysfunction could not be examined with these data.

Both databases are single-country and English-language, so multi-ethnic validation is needed before the findings can be generalised.

Subgroup analyses were not adjusted for multiplicity and should be regarded as exploratory.

A definitive answer will require prospective randomised trials in patients with hepatic failure.

Conclusions

In ICU patients with hepatic failure (n = 2358), compared with propofol, midazolam was independently associated with higher 28-day mortality (HR 1.48, 95% CI 1.30–1.69, $P < 0.001$) and dexmedetomidine with lower 28-day mortality (HR 0.56, 95% CI 0.45–0.69, $P < 0.001$) after multivariable adjustment and inverse-probability weighting. The midazolam association was concordant in an independent critical care database, and all estimates were unchanged across the pre-specified subgroups and nine alternative analytic specifications. These observational findings should be regarded as hypothesis-generating; a prospective randomised trial comparing dexmedetomidine with propofol or midazolam in patients with hepatic failure is warranted.

Abbreviations

AKI

acute kidney injury

APACHE II

Acute Physiology and Chronic Health Evaluation II

ATO

average treatment effect in the overlap population

BMI

body mass index

CI

confidence interval

CRRT

continuous renal replacement therapy

eICU-CRD

eICU Collaborative Research Database

HE

hepatic encephalopathy

HR

hazard ratio

ICD

International Classification of Diseases
ICU
intensive care unit
IPTW
inverse-probability-of-treatment weighting
IQR
interquartile range
MELD
model for end-stage liver disease
MIMIC-IV
Medical Information Mart for Intensive Care IV
NDE
natural direct effect
NIE
natural indirect effect
OR
odds ratio
RASS
Richmond Agitation-Sedation Scale
RR
risk ratio
SOFA
Sequential Organ Failure Assessment
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

This study used two fully de-identified, publicly available critical care databases (MIMIC-IV v3.1 and eICU-CRD). Data collection for MIMIC-IV was approved by the Institutional Review Boards of the Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology, which waived the requirement for informed consent; the eICU-CRD is distributed by Philips Healthcare after de-identification. No additional ethics approval or informed consent was therefore required for this secondary analysis.

Consent for publication

Not applicable.

Availability of data and materials

MIMIC-IV v3.1 and the eICU-CRD are available to credentialed users through PhysioNet (<https://physionet.org/content/mimiciv/> and <https://physionet.org/content/eicu-crd/>) after completion of the required training and data-use agreements. The derived analysis dataset and the analysis code that support the findings of this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Chang Liu and Huamin Wang contributed equally to this work and are co-first authors. Chang Liu: conceptualisation, methodology, formal analysis, writing - original draft. Huamin Wang: methodology, data curation, formal analysis, writing - original draft. Renkun Wang: data curation, software, validation. Haijin Wen: data curation, visualisation. Guozhi Liu: investigation, resources. Liufang Hu: investigation, resources. Yan Liu: validation, formal analysis. Yali Luo: validation, data curation. Huibing Chen: conceptualisation, supervision, project administration, funding acquisition, writing - review and editing. All authors read and approved the final manuscript.

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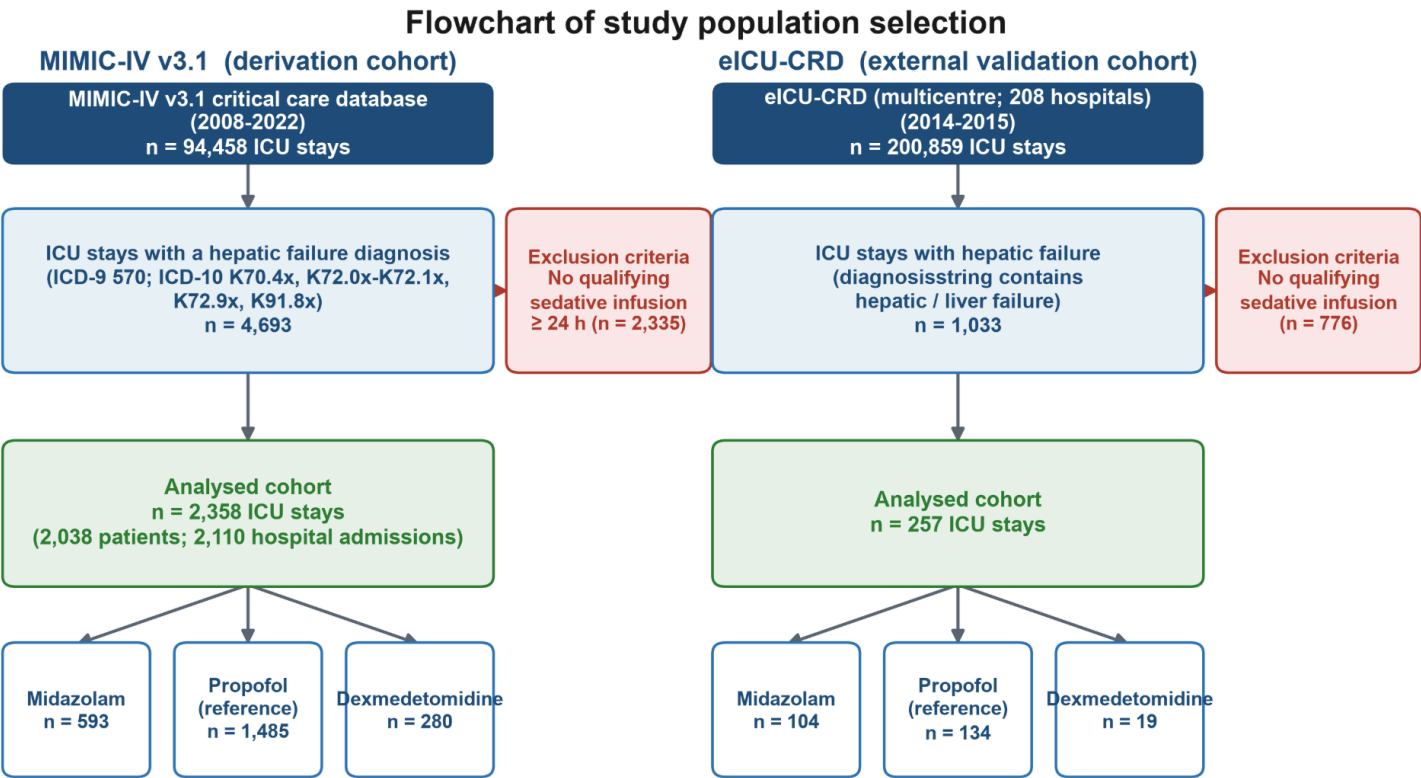
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Figures



ICU, intensive care unit; eICU-CRD, eICU Collaborative Research Database. Numbers denote ICU stays unless stated otherwise.

Figure 1

Flowchart of study population selection. MIMIC-IV v3.1 (derivation cohort; left) and eICU-CRD (external validation cohort; right). ICU, intensive care unit; eICU-CRD, eICU Collaborative Research Database.

28-day Mortality — Kaplan-Meier by Sedation Group
(Log-rank P = <0.001)

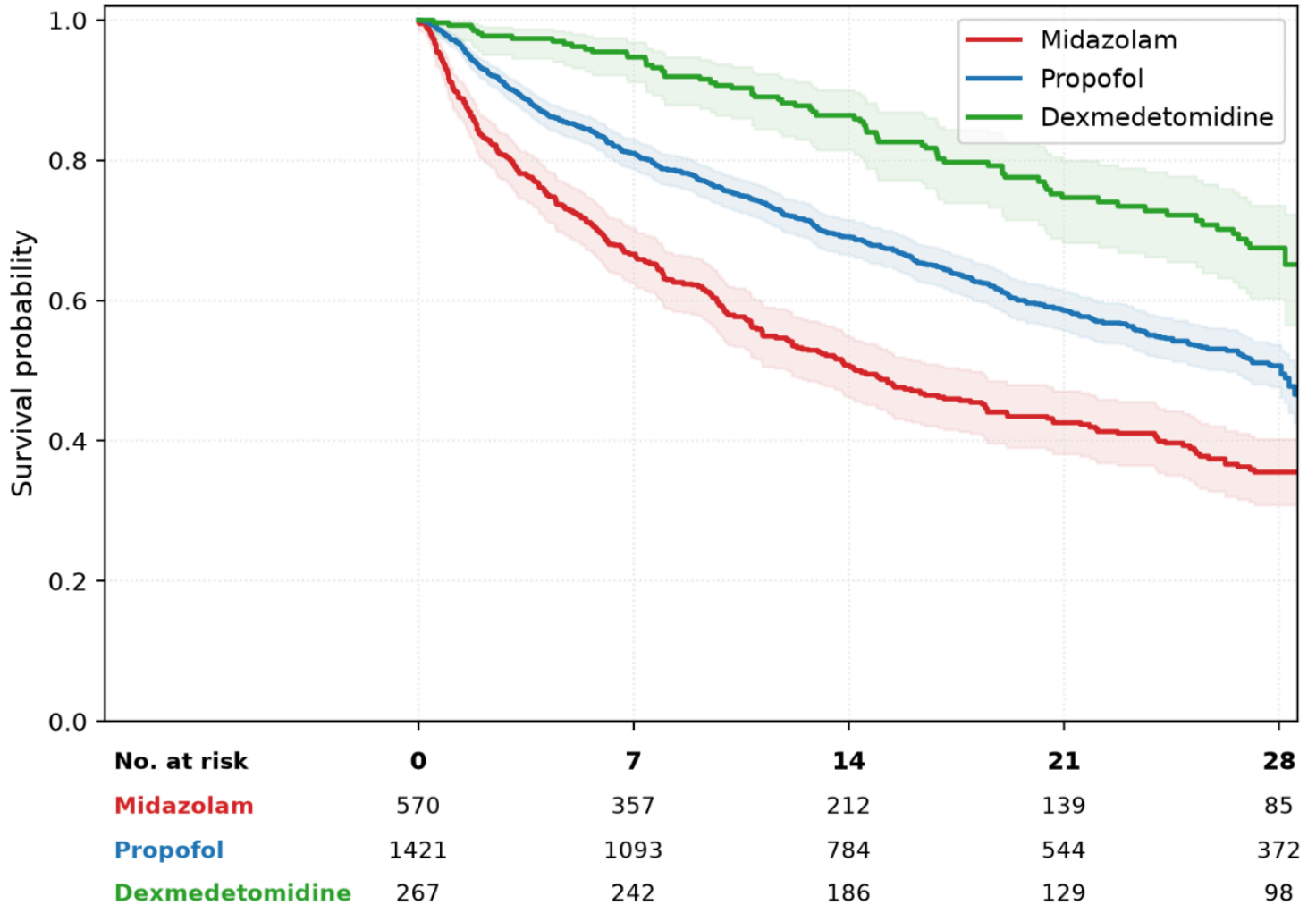


Figure 2

Kaplan-Meier estimates of 28-day survival by sedative group, with propofol as the reference. Shaded areas represent 95% confidence intervals; the number of patients at risk is shown below each panel.

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