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Sedation strategy and ICU Delirium: A multi-center, population-based propensity score-matched cohort study

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Objectives: We examined the relationship between dominant sedation strategy, risk of delirium and patient-centred outcomes in adults admitted to intensive care units(ICUs).

Design: Retrospective propensity matched cohort study.

Setting: Mechanically-ventilated adults (≥ 18 years) admitted to four Canadian hospital medical/surgical ICUs from 2014 – 2016 in Calgary, Alberta, Canada.

Participants: 2837 mechanically-ventilated adults (≥ 18 years) requiring admission to a medical/surgical ICU were evaluated for the relationship between sedation strategy and delirium.

Interventions: None.

Primary and secondary outcome measures: The primary exposure was dominant sedation strategy, defined as the sedative infusion, including midazolam, propofol or fentanyl, with the longest duration prior to first delirium assessment. The primary outcome was 'ever delirium' identified using the Intensive Care Delirium Screening Checklist (ICDSC). Secondary outcomes included mortality, length of stay (LOS), duration of ventilation and number of days with delirium. We analyzed the cohort with two propensity score (patient characteristics and therapies received) matched cohorts (propofol vs. fentanyl and propofol vs. midazolam).

Results: 2,837 patients (60.7% male; median age 57 years (interquartile range 43-68)) were considered for propensity matching. In propensity score-matched cohorts(propofol vs. midazolam, n=712; propofol vs. fentanyl, n=1,732), the odds of delirium were significantly higher with midazolam (odds ratio (OR) 1.46 (95% confidence interval(CI) 1.06-2.00)) and fentanyl (OR 1.22 (95% CI 1.00-1.48)) compared to propofol dominant sedation strategies. Dominant sedation strategy with midazolam and fentanyl were associated with longer duration of ventilation compared to propofol. Fentanyl was also associated with increased ICU mortality(OR 1.50 (1.07-2.12)) ICU and hospital LOS compared to a propofol dominant sedation strategy.

Conclusions: We identified a novel association between fentanyl dominant sedation strategies and increased risk of delirium, duration of mechanical ventilation, ICU LOS and hospital LOS. Midazolam dominant sedation strategies increased delirium risk and duration of mechanical ventilation.

Article Summary:

- We examine the effects of midazolam and fentanyl sedation strategies on delirium and patient centered outcomes using a large cohort of general intensive care patients.
- To reduce bias, we used a propensity score matching process on a large database.
- One key limitation is secondary to the concurrent use of multiple overlapping sedation strategies which may impact the results
- Based on the limitations and the nature of cohort studies, one should consider this study as hypothesis generating.

Introduction:

Delirium in critically ill patients is an acute confusional state marked by severe disorganization of cognition, fluctuating course, attentional deficit and awareness[1]. Older age, severity of illness, presence of mechanical ventilation, coma, and sedative medications place over 50% of ICU patients at risk for developing delirium[2-6]. Delirium in the ICU is common, and may prolong hospital stay, increase mortality risk and contribute to long term cognitive impairment[7 8]. With a burgeoning elderly population, ICU admission requiring mechanical ventilation is estimated to increase by 80% by 2026, therefore understanding potential contributors to delirium is paramount[9 10].

Over-sedation in the ICU, with benzodiazepines in particular, may be harmful[11,12]. Prospective cohort and randomized controlled trials support shorter durations of mechanical ventilation, more rapid awakening, and equally effective sedation with propofol or dexmedetomidine compared to midazolam[13-17]. Similarly, a population-based study by Lonardo *et al.* demonstrated higher mortality, longer duration of mechanical ventilation and longer ICU length of stay (LOS) in patients managed with benzodiazepines compared to propofol[11]. Lonardo *et al.* postulated midazolam's mortality effect may be may be due to increased rates of delirium. Delirium is associated with mortality, and some evidence supports patients treated with benzodiazepines may demonstrate higher rates of delirium in the ICU[8 13 18 19]. However, the association between benzodiazepines and delirium is inconsistent[6].

Sedation strategies often employ both a sedative, like propofol, and an analgesic, like fentanyl, simultaneously to achieve a desired effect. However, studies evaluating the clinical effects of these sedation strategies are lacking. Additional research is necessary to understand the effects of sedation strategies on delirium, hospital length of stay (LOS) and survival outcomes. Our study examined the relationship between dominant sedation strategy (continuously infused propofol, fentanyl, and/or midazolam), delirium and important patient-centred outcomes, in a multi-center population-based sample of mechanically-ventilated adults admitted to ICU.

Methods:

This retrospective cohort study was reported in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[20] and approved by the conjoint health research ethics board at the University of Calgary (REB17-0389).

Study Setting & Population:

We identified consecutive mechanical ventilated adults (≥ 18 years) admitted to four medical-surgical ICUs in Calgary, Alberta, Canada between January 1, 2014, to June 30th, 2016. Patients were excluded if:

1) Their ICU electronic health data did not link to an appropriate inpatient (hospital) admission
2) They did not have any ICU admissions with at least 1 Intensive Care Delirium Screening Checklist (ICDSC) assessment (details described in the *Outcome Measures* section)
3) They were non-Alberta residents (to allow for mortality outcome follow-up post hospital discharge)
4) They did not receive at least 1 continuous infusion of midazolam, propofol or fentanyl prior to the first ICDSC assessment.
5) They were never invasively ventilated during their ICU stay.
6) They did not have a single dominant continuous infusion prior to the first ICDSC assessment (see definition of dominant sedation strategy in the *Exposure Measure* section below for further detail).

If the patient was readmitted to ICU more than once during the study period, then only the first admission with at least 1 ICDSC assessment was used. The ICUs are staffed by accredited intensive care physicians which provide mechanical ventilation, vasoactive medications, and invasive monitoring.

Data sources:

Study data was derived from three electronic databases[21-23]. eCritical Alberta, a database and electronic medical record, that prospectively captures detailed clinical and demographic information[22]. The discharge abstract database (DAD) captures data on all hospitalized patients, including admission date, discharge, survival status, and up to 25 diagnostic codes from the International Classification of Diseases, 10th revision, Canadian enhancement. Out of hospital deaths were obtained from Alberta Vital Statistics, which captures all deaths occurring in Alberta. Data from Alberta Vital Statistics was available up to December 30, 2017, which provided at least 18 months of follow-up from the ICU admission date.

Exposures and Definitions:

The main study exposure was dominant sedation strategy prior to the first ICDSC assessment. A sedation strategy was defined as a continuous analgo-sedative infusion limited to midazolam, fentanyl, and propofol. Infusions were selected based on a screening survey which demonstrated small populations utilizing alternative sedation strategies. There were seven possible combinations for the sedation strategy prior to the first ICDSC assessment: 1) propofol only, 2) fentanyl only, 3) midazolam only, 4) propofol and fentanyl, 5) propofol and

midazolam, 6) fentanyl and midazolam, and 7) all three agents. A high number of patients received more than 1 agent, therefore we classified patients into a dominant sedation strategy, defined as the longest continuous duration of infusion prior to the first ICDSC assessment, which consists of three categories for the primary analyses. For example, if fentanyl was provided for the longest duration, fentanyl was considered the dominant sedation strategy. It is possible the patient could have received propofol or midazolam (or neither) for a duration less than fentanyl. If the patient received two agents for the same duration, the patient was excluded as no strategy was dominant. As sensitivity analyses, all seven possible combinations of the sedation strategy used prior to the first ICDSC assessment were considered.

Outcome Measures:

The primary outcome was categorized as 'ever/never delirium' during ICU admission compatible with previously established delirium outcome measures[7]. All ICU patients with a Richmond Agitation Sedation Scale(RASS)[24] score ≥-3 were evaluated twice daily using the ICDSC tool[25] and received a protocolized sedation awakening trial. The ICDSC is a validated delirium assessment tool[25]. Ever delirium patients were those with an *ICDSC score* ≥4; never delirium were those with an *ICDSC score* <4. Total number of days with an *ICDSC score* ≥4 defined delirium duration. Duration of delirium (days) was examined in secondary analyses.

Delirium motor subtypes were identified using the RASS, based on previously published criteria[18], and associated positive ICDSC score of ≥4. The scale is scored from -5 points (unarousable) to 0 points (calm) to +4 points (combative), where scores between -3 to 0 indicate hypoactive delirium, scores between 1 to 3 indicate hyperactive delirium, and scores that fluctuate between hypoactive and hyperactive indicate mixed delirium. All ICDSC scores ≥4 were linked to the closest RASS score within 4 hours of charting. If there was no RASS score documented within 4 hours of the ICDSC score, the sub-type was considered "unable to be classified". If there was a RASS score within 4 hours of the ICDSC score but the RASS was -5, -4 or +4, the sub-type was considered "unable to be assessed". If at least 1 assessment indicated hypoactive delirium and at least 1 assessment indicated hyperactive delirium the sub-type was considered mixed for that specific patient.

Secondary outcomes were mortality in the ICU and hospital, duration of mechanical ventilation, and ICU & hospital lengths of stay (LOS). Patient mortality was also reported at 30-days and 1-year. Duration of invasive mechanical ventilation was defined as the time a patient required the use of invasive ventilator.

Statistical Analysis:

Baseline characteristics were summarized using median with interquartile range (IQR) and frequency with percent and compared between sedation strategies using chi-squared tests and Kruskal-Wallis rank sum tests, as appropriate. For the primary outcome analysis, logistic regression was used to assess the association between dominant sedation strategy (propofol vs midazolam vs fentanyl) and risk of developing delirium. The relationship between dominant sedation strategy and delirium duration was analyzed using negative binomial models. The relationship between dominant sedation strategy and mortality outcomes were analyzed using logistic regression models. The relationship between dominant sedation strategy and LOS outcomes (ICU and hospital) were analyzed using linear regression models with a log-transformation of ICU LOS and hospital LOS. Primary analyses for all outcomes were based on forming two propensity score-matched cohorts: 1) propofol vs fentanyl and 2) propofol vs midazolam. Propensity scores were based on age, sex, reason for admission to ICU, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, use of vasoactive medications and use of continuous renal replacement therapy. The cohorts were formed based on 1:1 nearest-neighbor matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score[26]. Sensitivity analyses were based on the full cohort with models adjusted a priori for the same patient characteristics used in the propensity scores. The above analyses were repeated for the 7-category sedation strategy prior to the first ICDSC assessment. For these analyses, we formed six pairwise propensity score-matched cohorts similar to the primary analyses, matching with patients on propofol only for each of the other 6 categories of sedation strategy prior to the first ICDSC assessment. A two-sided p-value < 0.05 was considered statistically significant. Analyses were conducted in R, version 3.5.1.[27] Propensity-score matching was performed using the R package "MatchIt", version 3.0.2.

Results:

There were 2,837 patients in the study cohort (Figure 1). For those receiving propofol dominant sedation, it was common to receive a single agent (62.8%). While with fentanyl (14.8%) and midazolam dominant sedation strategies (34.8%) single agent use was less common. Most patients were male (60.7%) with a median age of 57 (IQR 43-68) years and admitted for a medical reason (50.4%). The median Charlson comorbidity score was 1 (IQR 0-2), admission SOFA score 7 (IQR 4-9) and admission APACHE II score 19 (IQR 14-25). Patients who received a midazolam dominant sedation strategy were more likely admitted for medical reasons (72.8%) and had higher Charlson comorbidity scores, admission SOFA scores and admission APACHE II scores than those receiving

propofol and fentanyl dominant sedation strategies. Patients receiving midazolam dominant strategies were also more likely to receive vasoactive medications (68.8%) compared to those predominantly receiving propofol (45.3%) and fentanyl dominant sedation strategies (64.5%). (Table 1)

Due to missing patient characteristics for 5 patients (0.2%), propensity scores were calculated for 1,409 patients receiving propofol dominant strategies, 1,067 patients receiving fentanyl dominant sedation strategies and 356 patients receiving midazolam dominant sedation strategies. Of the patients receiving fentanyl dominant sedation strategies, 201 (18.8%) could not be matched to a patient receiving propofol dominant sedation strategies within the specified caliper width of 0.2; therefore, this resulted in a matched cohort for propofol and fentanyl of 1,732 patients. Of the patients receiving midazolam dominant sedation strategies, all 356 patients could be matched to a patient receiving propofol dominant sedation strategies; therefore, this resulted in a matched cohort for patients with propofol and midazolam dominant sedation strategies of 712 patients. After matching, the baseline characteristics were balanced(Table 1).

In the propensity score-matched cohorts, there was a statistically significant association between delirium and midazolam dominant(odds ratio[OR] 1.46 (95% confidence interval 1.06-2.00); p=0.02) as well as fentanyl dominant (OR 1.22 (95% CI 1.00-1.48); p=0.05) sedation strategies compared to propofol dominant sedation strategies(Figure 2). Sensitivity analyses based on the 7-category sedation strategy prior to the first ICDSC assessment showed an increased odds of delirium for those on more than one agent compared to those on propofol only (Table 2). Among those who ever experienced delirium, the distribution of delirium subtypes was similar between dominant sedation strategies (Table 3). Based on the propensity score-matched cohorts, a fentanyl dominant sedation strategy was associated with longer duration of mechanical ventilation, longer ICU and hospital LOS and more delirium days compared to a propofol dominant sedation strategy, while a midazolam dominant sedation strategy was associated with a longer duration of mechanical ventilation compared to a propofol dominant sedation strategy(Figure 3). Sensitivity analyses of the secondary outcomes based on the 7-category sedation strategy can be found in the supplementary results(Supplementary Digital Content - Table 1). There was a statistically significant association between fentanyl dominant sedation strategy and ICU(OR=1.50 (1.07-2.12)) and 30-day mortality(OR=1.35 (1.02-1.79)) in propensity score-matched analyses(Supplementary Digital Content - Table 2).

Discussion:

Sedative strategy may increase the risk of adverse patient complications such as delirium, or prolonged mechanical ventilation. We found a midazolam dominant sedation strategy was associated with increased risk of developing delirium, and duration of mechanical ventilation, however was not associated with mortality. Conversely, fentanyl was associated with multiple detrimental outcomes including increased risk of ICU & hospital LOS and duration of mechanical ventilation while the associations with delirium and mortality appeared inconsistent. Regardless, these results should advise clinicians to be cautious when selecting their sedation strategy.

The association between benzodiazepine-based sedation strategies and delirium has been suggested in prior literature [8 17 18]. The importance of these findings should not be understated as patients with delirium suffer prolonged hospital stays, an increased risk of mortality and long term cognitive impairment[7 8]. Sedation using multiple agents also increased delirium risk, duration of mechanical ventilation, ICU LOS and hospital LOS. Whether these effects are a direct result from the sedation strategy, or from the resulting delirium are unclear. Therefore, avoiding benzodiazepine dominant and multi-agent sedation strategies may minimize delirium risk.

We also re-confirmed the association between midazolam dominant sedation strategies and longer mechanical ventilation but not mortality as reported by Lonardo *et al.*[11]. The mechanism that benzodiazepines would increase mortality is unclear, however prolonged mechanical ventilation is a known risk factor for mortality[28]. A meta-analysis by Ho *et al.* comparing propofol to other sedation strategies did not demonstrate an impact on mortality; however, it did not specifically look at midazolam compared to other benzodiazpines[29]. The heterogeneity in mortality outcomes may be attributable to variation in sedation depth, as early deep sedation is an independent predictor of delayed time to extubation and long term mortality[12]. Therefore, not only agent choice but also sedation depth might contribute to the variation in mortality risk observed with benzodiazepines.

Sedation with midazolam and fentanyl is often selected for patients with significant hemodynamic instability to avoid the negative ionotropic and vasodilatory effects of propofol. In our study, those receiving midazolam dominant sedation strategies demonstrated significantly higher SOFA scores, APACHE II scores on admission and were more likely to receive vasoactive medications and continuous renal replacement. All of these may impact mortality when unaccounted for and may explain the heterogeneity observed in the literature[30]. For example, Lonardo *et al.* did not control for the presence of renal replacement which has been associated with a high rate of mortality in critically ill patients[11 31]. Our use of detailed clinical data for risk adjustment may help explain the differences in mortality compared to prior reports.

A fentanyl dominant sedation strategy was significantly associated with increased ICU LOS, hospital LOS and duration of mechanical ventilation. Prior literature shows associations with delayed extubation when given in the first 48 hours, which would support our findings[12]. What is unclear is whether our result is a direct effect of fentanyl or a synergistic combination of both fentanyl and midazolam. Moreover, fentanyl dominant strategies were associated with increased risk of ICU mortality, 30-day mortality, and at hospital discharge but not 1 year. It is difficult to know what to make of these observations. The relationship between fentanyl use and ICU mortality has been incompletely explored in the literature. The mortality risk associated with fentanyl use may be attributable to prolongations in mechanical ventilation[28]. In our data, the effect of mortality appeared strongest in those receiving only fentanyl and was less robust when used in combination. Another possibility could be the immunomodulatory effects of naroctics. The mu-opioid receptor is expressed on macrophages and T-lymphocytes, and chronic administration may increase the risk of bacterial infection[32-34]. Therefore, large doses of fentanyl may contribute to further immune dysregulation thereby placing critically ill patients at risk of infection. A final possibility is the use of fentanyl in the provision of palliative symptom control, therefore the mortality association is a marker of this practice. Further study is required to better delineate the true nature of the association between fentanyl and deleterious patient outcomes in the ICU.

Our studies strength is our large cohort size supported by granular patient detail extracted from a prospectively collected, clinical database representing multiple ICUs and the covariates were rigorously controlled using a propensity matched model[22]. The multicenter study design provides a pragmatic view of how sedation strategies are utilized in clinical practice. Limitations of our study include the possibility of confounding bias due to unmeasured impactful covariates or confounding by indication. Patients receiving midazolam dominant strategies were clearly more critically ill compared to those receiving propofol dominant strategies manifest by higher APACHE II scores, greater vasopressor requirements, and higher rates of renal replacement. To compensate, we conducted propensity score-matched analyses adjusted for known covariates. Additionally, fentanyl and midazolam are often used concurrently. Clearly teasing apart the isolated effects of each medication may be challenging. Adjustment with our statistical model should minimize this effect, however randomized controlled trials would better assess this limitation. Moreover, we focused primarily on the presence or absence of continuous infusions and did not quantify the impact of independent drug boluses. However, this effect would lessen the association with our primary outcome suggesting our observed associations are conservative. Another limitation is the use of drug

duration as a surrogate for the impact of the sedation strategy rather than in vivo plasma concentrations. Patient factors may impact midazolam metabolism due to differences in age, hepatic or renal dysfunction or co-administration of medications with similar metabolic pathways[35-37]. Finally, the definition of dominant sedation strategy based on longest duration of infusion prior to first ICDSC may be considered arbitrary. However, defining sedation in the setting of multiple agents has been incompletely explored in the literature, therefore novel definitions are required. Our data closely reflects multiple findings previously reported with both midazolam and fentanyl sedation. This reduces the possibility our findings are pure chance.

Conclusion:

This multi-center, propensity score-matched cohort study demonstrates a novel association between fentanyl dominant sedation strategies and negative outcomes in the ICU. Fentanyl dominant sedation strategies were associated with increased risk of delirium, duration of ventilation, ICU LOS and hospital LOS. We also confirmed previous reports including an increased risk of delirium and duration of mechanical ventilation with midazolam dominant sedation strategies. This study highlights the need for additional research to further evaluate potentially negative effects of fentanyl and midazolam based sedation strategies.

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No patient involved.

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Tables:

Table 1: Baseline Characteristics

	Overall cohort			**Dominant sedation strategy matched cohorts**			
				Propofol vs. Midazolam matched cohort		Propofol vs. Fentanyl matched cohort	
	Propofol (n=1412)	Fentanyl (n=1069)	Midazolam (n=356)	Propofol (n=356)	Midazolam (n=356)	Propofol (n=866)	Fentanyl (n=866)
Characteristic							
Age, median (IQR)	56 (42-67)	59 (44-69)	59 (46-71)	58 (48-69)	59 (46-71)	57 (46-68)	57 (42-69)
Male, n (%)	843 (59.7)	656 (61.4)	223 (62.6)	227 (63.8)	223 (62.6)	533 (61.5)	520 (60.0)
Admission reason, n (%)							
Medical	791 (56.0)	379 (35.5)	259 (72.8)	253 (71.1)	259 (72.8)	426 (49.2)	379 (43.8)
Surgical	265 (18.8)	405 (37.9)	69 (19.4)	74 (20.8)	69 (19.4)	256 (29.6)	248 (28.6)
Neurological	245 (17.4)	73 (6.8)	19 (5.3)	18 (5.1)	19 (5.3)	76 (8.8)	73 (8.4)
Trauma	109 (7.7)	211 (19.7)	9 (2.5)	11 (3.1)	9 (2.5)	108 (12.5)	166 (19.2)
Location admitted from							

Emergency Room	833 (59.0%)	413 (38.6%)	190 (53.4%)	202 (56.7)	190 (53.4)	441 (50.9)	369 (42.6)
Operating Room/Recovery	278 (19.7%)	399 (37.3%)	59 (16.6%)	63 (17.7)	59 (16.6)	232 (26.8)	271 (31.3)
Hospital Ward	254 (18.0%)	209 (19.6%)	91 (25.6%)	85 (23.9)	91 (25.6)	165 (19.1)	180 (20.8)
Another Hospital	26 (1.8%)	24 (2.2%)	7 (2.0%)	4 (1.1)	7 (2.0)	17 (2.0)	23 (2.7)
Other	21 (1.5%)	24 (2.2%)	9 (2.5%)	2 (0.6)	9 (2.5)	11 (1.3)	23 (2.7)
Charlson score, n (%)							
0	582 (41.2%)	422 (39.5%)	121 (34.0%)	127 (35.7)	121 (34.0)	322 (37.2)	336 (38.8)
1	317 (22.5%)	239 (22.4%)	70 (19.7%)	61 (17.1)	70 (19.7)	201 (23.2)	207 (23.9)
2+	513 (36.3%)	408 (38.2%)	165 (46.3%)	168 (47.2)	165 (46.3)	343 (39.6)	323 (37.3)
Charlson score, median (IQR)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-2)
Admission SOFA score, median (IQR)	6 (4-8)	7 (5-10)	8 (6-11)	8 (5-10)	8 (6-11)	7 (4-9)	7 (4-10)
Admission APACHE II score, median (IQR)	18 (13-24)	19 (14-25)	23 (16-28)	21 (16-27)	23 (16-28)	19 (14-24)	19 (13-26)
Vasoactive medications, n (%)	639 (45.3%)	690 (64.5%)	245 (68.8%)	241 (67.7)	245 (68.8)	526 (60.7)	488 (56.4)
Continuous renal replacement therapy, n (%)	59 (4.2%)	78 (7.3%)	33 (9.3%)	28 (7.9)	33 (9.3)	52 (6.0)	73 (8.4)

Table 2: Sensitivity Analyses examining the relationship between delirium and individual sedation agents prior to first ICDSC assessment

	Overall Cohort			**Matched cohorts**			
Sedation agent prior to first ICDSC assessment	**Number of patients**	**Ever Delirium, n (%)**	**Adjusted OR (95% CI)[1]**	**Number of patients per group**	**Ever Delirium for propofol patients from matched cohorts, n (%)**	**Ever Delirium, n (%)**	**Propensity score-matched OR for Ever delirium(95% CI)[2]**
Propofol	887	509 (57.4)	1.00 (reference group)	N/A[3]	N/A[3]	N/A[3]	1.00 (reference group)
Fentanyl	158	91 (57.6)	1.04 (0.71-1.52)	152	74 (48.7)	87 (57.2)	1.23 (0.74-2.05)
Midazolam	124	77 (62.1)	1.11 (0.73-1.69)	122	69 (56.6)	75 (61.5)	1.41 (0.90-2.22)
Propofol + Fentanyl	854	543 (63.6)	1.32 (1.06-1.65)	565	323 (57.2)	347 (61.4)	1.19 (0.94-1.51)
Propofol + Midazolam	224	163 (72.8)	1.72 (1.23-2.43)	223	143 (64.1)	162 (72.6)	1.49 (1.00-2.23)
Fentanyl + Midazolam	222	160 (72.1)	1.72 (1.22-2.46)	214	119 (55.6)	153 (71.5)	2.00 (1.34-3.00)
All 3	368	269 (73.1)	1.84 (1.38-2.47)	335	199 (59.4)	241 (71.9)	1.75 (1.27-2.42)

[1]Adjusted for age, sex, admission class, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, vasoactive medications, continuous renal replacement therapy
[2]Propensity scores based on age, sex, admission class, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, vasoactive medications, continuous renal replacement therapy. 1:1 nearest-neighbor pairwise (propofol vs. fentanyl and propofol vs. midazolam, etc.) matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score
[3]The propofol group was used to form all 6 matched cohorts and therefore the number of patients and number (%) experiencing delirium for propofol varies for each comparison

Table 3: Delirium subtype by dominant sedation strategy prior to first ICDSC assessment among patients experiencing delirium for the propensity score-matched cohorts

	Dominant sedation strategy			
	Propofol vs. Fentanyl matched cohort patients experiencing delirium		Propofol vs. Midazolam matched cohort patients experiencing delirium	
Delirium Subtype	Propofol (n=529)	Fentanyl (n=569)	Propofol (n=228)	Midazolam (n=257)
Hyperactive only, n (%)	47 (8.9)	40 (7.0)	15 (6.6)	25 (9.7)
Hypoactive only, n (%)	210 (39.7)	228 (40.1)	104 (45.6)	106 (41.2)
Mixed, n (%)	254 (48.0)	289 (50.8)	103 (45.2)	123 (47.9)
Unable to assess or classify, n (%)	18 (3.4)	12 (2.1)	6 (2.6)	3 (1.2)

Figure 1: Cohort diagram

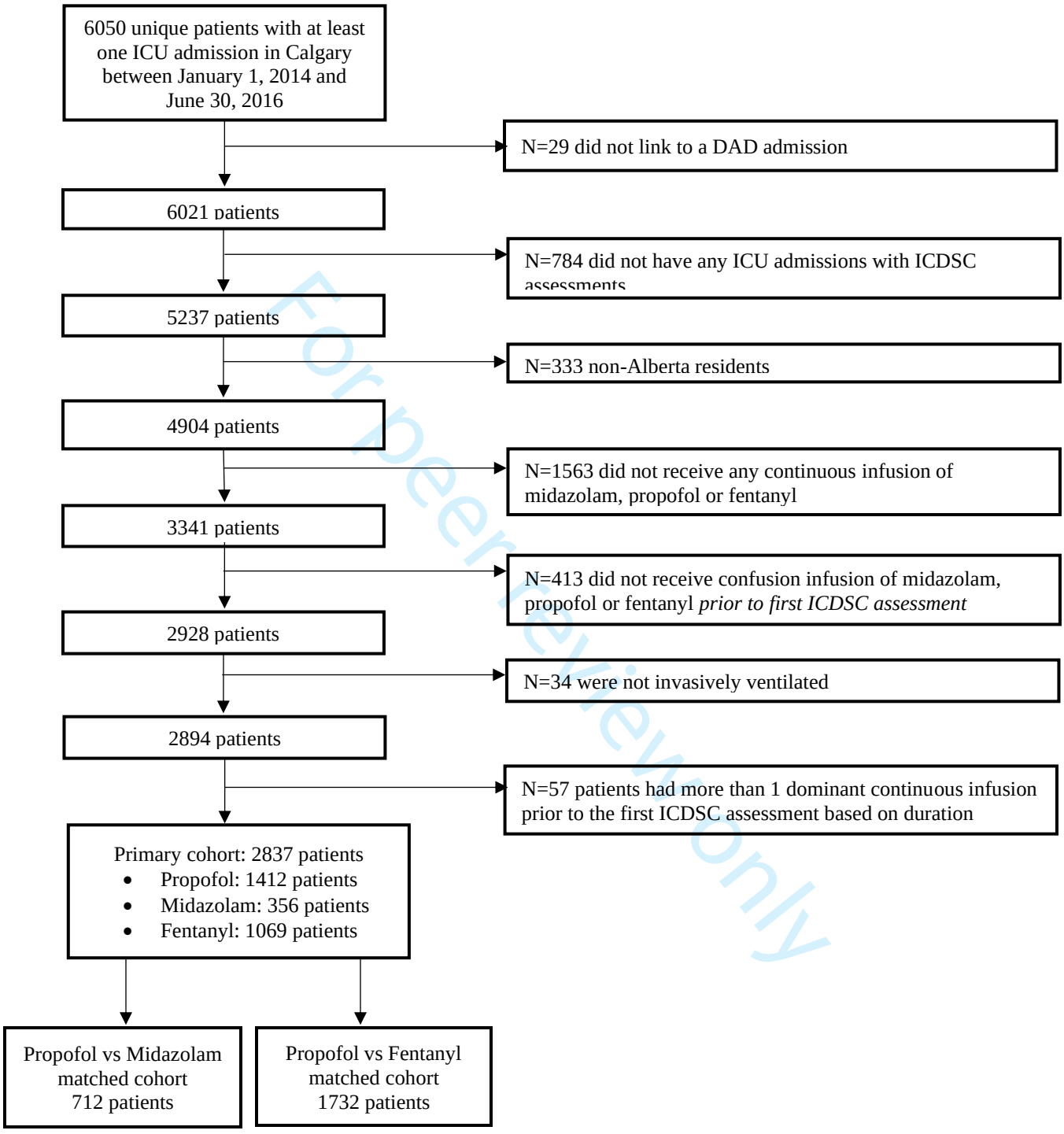

Figure 2: Propensity score-matched odds ratios of delirium by dominant sedation strategy prior to first ICDSC assessment

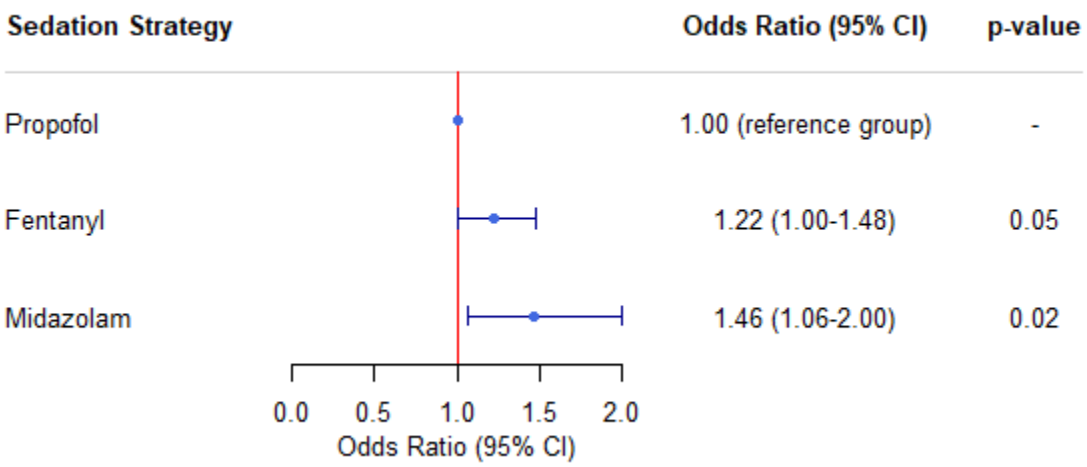

Figure 3: Forest plot of propensity score-matched mean or rate ratios of secondary outcomes and sedation strategy

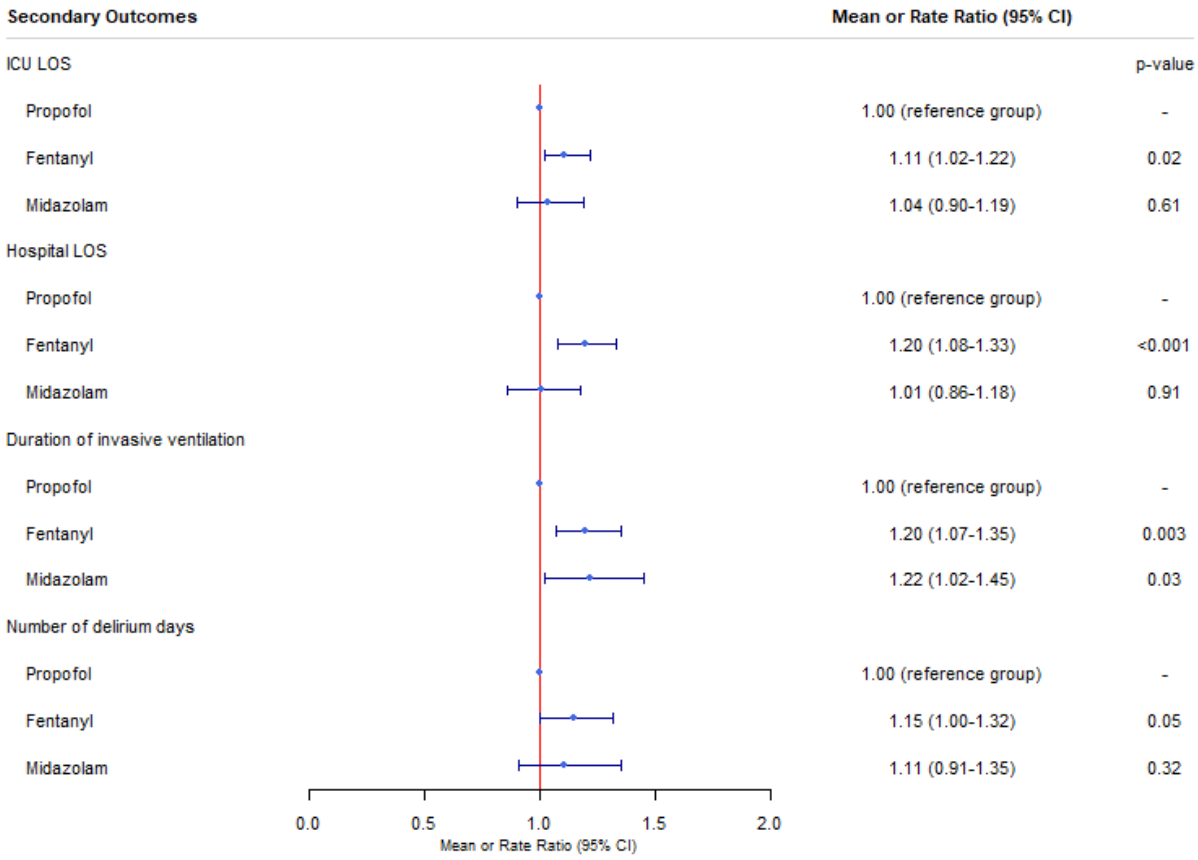

Table S1: Secondary outcomes by sedation strategy prior to first ICDSC assessment

Propensity score-matched mean ratio or rate ratio (95% CI)[1]	**ICU LOS**	**Hospital LOS**	**Duration of invasive ventilation**	**Number of delirium days**
Sedation prior to first ICDSC assessment				
Propofol	1.00 (reference group)	1.00 (reference group)	1.00 (reference group)	1.00 (reference group)
Fentanyl	1.06 (0.85-1.33)	1.25 (0.97-1.61)	1.00 (0.74-1.35)	1.03 (0.69-1.55)
Midazolam	0.83 (0.65-1.06)	0.98 (0.75-1.28)	1.00 (0.73-1.38)	0.88 (0.59-1.31)
Propofol + Fentanyl	**1.17 (1.05-1.30)**	**1.20 (1.05-1.38)**	**1.37 (1.18-1.58)**	1.08 (0.90-1.31)
Propofol + Midazolam	1.16 (0.99-1.36)	0.86 (0.68-1.08)	**1.59 (1.28-1.99)**	1.11 (0.87-1.41)
Fentanyl + Midazolam	**1.40 (1.17-1.67)**	**1.27 (1.02-1.57)**	**1.95 (1.54-2.46)**	1.28 (0.97-1.69)
All 3	**1.73 (1.52-1.98)**	**1.39 (1.18-1.63)**	**2.47 (2.06-2.97)**	**1.35 (1.10-1.67)**

[1]Propensity score based on age, sex, admission class, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, vasoactive medications, continuous renal replacement therapy. 1:1 nearest-neighbor matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score

Table S2: Propensity score matched models of the relationship between mortality outcomes and dominant sedation strategy prior to first ICDSC assessment

Outcome	Dominant Sedation Strategy	Mortality, n (%)	Propensity score-matched OR (95% CI)[2]
ICU Mortality	Propofol	94 (6.7)	1.00 (reference)
	Fentanyl	104 (9.7)	**1.50 (1.07-2.12)**
	Midazolam	39 (11.0)	1.20 (0.74-1.97)
Hospital Mortality	Propofol	157 (11.1)	1.00 (reference)
	Fentanyl	166 (15.5)	1.27 (0.97-1.67)
	Midazolam	59 (16.6)	1.14 (0.76-1.70)
Died within 30 days of ICU admission	Propofol	148 (10.5)	1.00 (reference)
	Fentanyl	148 (13.8)	**1.35 (1.02-1.79)**
	Midazolam	50 (14.0)	1.02 (0.67-1.57)
Died within 1 year of ICU admission	Propofol	268 (19.0)	1.00 (reference)
	Fentanyl	248 (23.2)	1.13 (0.90-1.43)
	Midazolam	91 (25.6)	1.01 (0.72-1.42)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, 6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6, Supplement methods
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	4, 7 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	7 Table 2, 3,

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2,3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Sedation strategy and ICU Delirium: A multi-center, population-based propensity score-matched cohort study

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Figures: 3

Conflicts of Interest: No author has a conflict of interest to declare.

Keywords: Delirium, ICU sedation, fentanyl sedation, midazolam sedation

Objectives: We examined the relationship between dominant sedation strategy, risk of delirium and patient-centred outcomes in adults admitted to intensive care units(ICUs).

Design: Retrospective propensity matched cohort study.

Setting: Mechanically-ventilated adults (≥ 18 years) admitted to four Canadian hospital medical/surgical ICUs from 2014 – 2016 in Calgary, Alberta, Canada.

Participants: 2837 mechanically-ventilated adults (≥ 18 years) requiring admission to a medical/surgical ICU were evaluated for the relationship between sedation strategy and delirium.

Interventions: None.

Primary and secondary outcome measures: The primary exposure was dominant sedation strategy, defined as the sedative infusion, including midazolam, propofol or fentanyl, with the longest duration prior to first delirium assessment. The primary outcome was 'ever delirium' identified using the Intensive Care Delirium Screening Checklist (ICDSC). Secondary outcomes included mortality, length of stay (LOS), duration of ventilation and number of days with delirium. We analyzed the cohort with two propensity score (patient characteristics and therapies received) matched cohorts (propofol vs. fentanyl and propofol vs. midazolam).

Results: 2,837 patients (60.7% male; median age 57 years (interquartile range 43-68)) were considered for propensity matching. In propensity score-matched cohorts(propofol vs. midazolam, n=712; propofol vs. fentanyl, n=1,732), the odds of delirium were significantly higher with midazolam (odds ratio (OR) 1.46 (95% confidence interval(CI) 1.06-2.00)) and fentanyl (OR 1.22 (95% CI 1.00-1.48)) compared to propofol dominant sedation strategies. Dominant sedation strategy with midazolam and fentanyl were associated with longer duration of ventilation compared to propofol. Fentanyl was also associated with increased ICU mortality(OR 1.50 (1.07-2.12)) ICU and hospital LOS compared to a propofol dominant sedation strategy.

Conclusions: We identified a novel association between fentanyl dominant sedation strategies and an increased risk of delirium, a composite outcome of delirium or death, duration of mechanical ventilation, ICU LOS and hospital LOS. Midazolam dominant sedation strategies increased delirium risk and duration of mechanical ventilation.

Article Summary:

- We examine the effects of midazolam and fentanyl sedation strategies on delirium and patient centered outcomes using a large cohort of general intensive care patients.
- To reduce bias, we used a propensity score matching process on a large database.
- One key limitation is secondary to the concurrent use of multiple overlapping sedation strategies which may impact the results
- Based on the limitations and the nature of cohort studies, one should consider this study as hypothesis generating.

Introduction:

Delirium in critically ill patients is an acute confusional state marked by severe disorganization of cognition, fluctuating course, attentional deficit and a disturbance of awareness[1]. Older age, severity of illness, presence of mechanical ventilation, coma, and sedative medications place over 50% of ICU patients at risk for developing delirium[2-6]. Delirium in the ICU is common, and may prolong hospital stay, increase mortality risk and contribute to long term cognitive impairment[7 8]. With a burgeoning elderly population, ICU admission requiring mechanical ventilation is estimated to increase by 80% by 2026, therefore understanding potential contributors to delirium is paramount[9 10].

Over-sedation in the ICU, with benzodiazepines in particular, may be harmful[11,12]. Prospective cohort and randomized controlled trials support shorter durations of mechanical ventilation, more rapid awakening with propofol or dexmedetomidine compared to midazolam [13-17]. Similarly, a population-based study by Lonardo *et al.* demonstrated higher mortality, longer duration of mechanical ventilation and longer ICU length of stay (LOS) in patients managed with benzodiazepines compared to propofol[11]. Lonardo *et al.* postulated midazolam's mortality effect may be due to increased rates of delirium. Delirium is associated with mortality, and some evidence supports patients treated with benzodiazepines may demonstrate higher rates of delirium in the ICU[8 13 18 19]. However, the association between benzodiazepines and delirium is inconsistent[6].

Sedation strategies often employ both a sedative, like propofol, and an analgesic, like fentanyl, simultaneously to achieve a desired effect. However, studies evaluating the clinical effects of these sedation strategies are lacking. Additional research is necessary to understand the effects of sedation strategies on delirium, hospital length of stay (LOS) and survival outcomes. Our study examined the relationship between dominant sedation strategy (continuously infused propofol, fentanyl, and/or midazolam), delirium and important patient-centred outcomes, in a multi-center population-based sample of mechanically-ventilated adults admitted to ICU.

Methods:

Ethics Approval Statement:

This retrospective cohort study was reported in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[20] and approved by the conjoint health research ethics board at the University of Calgary (REB17-0389).

Patient & Public Involvement Statement:

Neither patients, nor the public were not involved in the design, collection, compilation or completion of this research study.

Study Setting & Population:

We identified consecutive mechanical ventilated adults (≥ 18 years) admitted to four medical-surgical ICUs in Calgary, Alberta, Canada between January 1, 2014, to June 30th, 2016. Patients were excluded if:

1) Their ICU electronic health data did not link to an appropriate inpatient (hospital) admission
2) They did not have any ICU admissions with at least 1 Intensive Care Delirium Screening Checklist (ICDSC) assessment (details described in the *Outcome Measures* section)
3) They were non-Alberta residents (to allow for mortality outcome follow-up post hospital discharge)
4) They did not receive at least 1 continuous infusion of midazolam, propofol or fentanyl prior to the first ICDSC assessment.
5) They were never invasively ventilated during their ICU stay.
6) They did not have a single dominant continuous infusion prior to the first ICDSC assessment (see definition of dominant sedation strategy in the *Exposure Measure* section below for further detail).

If the patient was readmitted to ICU more than once during the study period, then only the first admission with at least 1 ICDSC assessment was used. The ICUs are staffed by accredited intensive care physicians which provide mechanical ventilation, vasoactive medications, and invasive monitoring.

Data sources:

Study data was derived from three electronic databases[21-23]. eCritical Alberta, a database and electronic medical record, that prospectively captures detailed clinical and demographic information[22]. The discharge abstract database (DAD) captures data on all hospitalized patients, including admission date, discharge, survival status, and up to 25 diagnostic codes from the International Classification of Diseases, 10th revision, Canadian enhancement. Out of hospital deaths were obtained from Alberta Vital Statistics, which captures all deaths occurring in Alberta. Data from Alberta Vital Statistics was available up to December 30, 2017, which provided at least 18 months of follow-up from the ICU admission date.

Exposures and Definitions:

The main study exposure was dominant sedation strategy prior to the first ICDSC assessment. A sedation strategy was defined as a continuous analgo-sedative infusion limited to midazolam, fentanyl, and propofol.

Infusions were selected based on a screening survey which demonstrated small populations utilizing alternative sedation strategies. There were seven possible combinations for the sedation strategy prior to the first ICDSC assessment: 1) propofol only, 2) fentanyl only, 3) midazolam only, 4) propofol and fentanyl, 5) propofol and midazolam, 6) fentanyl and midazolam, and 7) all three agents. A high number of patients received more than 1 agent, therefore we classified patients into a dominant sedation strategy, defined as the longest continuous duration of infusion prior to the first ICDSC assessment, which consists of three categories for the primary analyses. For example, if fentanyl was provided for the longest duration, fentanyl was considered the dominant sedation strategy. It is possible the patient could have received propofol or midazolam (or neither) for a duration less than fentanyl. If the patient received two agents for the same duration, the patient was excluded as no strategy was dominant. As sensitivity analyses, all seven possible combinations of the sedation strategy used prior to the first ICDSC assessment were considered.

Outcome Measures:

The primary outcome was categorized as 'ever/never delirium' during ICU admission compatible with previously established delirium outcome measures[7]. All ICU patients with a Richmond Agitation Sedation Scale(RASS)[24] score ≥-3 were evaluated twice daily using the ICDSC tool[25] and received a protocolized sedation awakening trial. The ICDSC is a validated delirium assessment tool[25]. Ever delirium patients were those with an *ICDSC score* ≥4; never delirium were those with an *ICDSC score* <4. Total number of days with an *ICDSC score* ≥4 defined delirium duration. Duration of delirium (days) was examined in secondary analyses.

Delirium motor subtypes were identified using the RASS, based on previously published criteria[18], and associated positive ICDSC score of ≥4. The scale is scored from -5 points (unarousable) to 0 points (calm) to +4 points (combative), where scores between -3 to 0 indicate hypoactive delirium, scores between 1 to 3 indicate hyperactive delirium, and scores that fluctuate between hypoactive and hyperactive indicate mixed delirium. All ICDSC scores ≥4 were linked to the closest RASS score within 4 hours of charting. If there was no RASS score documented within 4 hours of the ICDSC score, the sub-type was considered "unable to be classified". If there was a RASS score within 4 hours of the ICDSC score but the RASS was -5, -4 or +4, the sub-type was considered "unable to be assessed". If at least 1 assessment indicated hypoactive delirium and at least 1 assessment indicated hyperactive delirium the sub-type was considered mixed for that specific patient.

Secondary outcomes were mortality in the ICU and hospital, duration of mechanical ventilation, and ICU & hospital lengths of stay (LOS). Patient mortality was also reported at 30-days and 1-year. Duration of invasive mechanical ventilation was defined as the time a patient required the use of invasive ventilator.

Statistical Analysis:

Baseline characteristics were summarized using median with interquartile range (IQR) and frequency with percent and compared between sedation strategies using chi-squared tests and Kruskal-Wallis rank sum tests, as appropriate. For the primary outcome analysis, logistic regression was used to assess the association between dominant sedation strategy (propofol vs midazolam vs fentanyl) and risk of developing delirium. The relationship between dominant sedation strategy and delirium duration was analyzed using negative binomial models. The relationship between dominant sedation strategy and mortality outcomes were analyzed using logistic regression models. The relationship between dominant sedation strategy and LOS outcomes (ICU and hospital) were analyzed using linear regression models with a log-transformation of ICU LOS and hospital LOS. Primary analyses for all outcomes were based on forming two propensity score-matched cohorts: 1) propofol vs fentanyl and 2) propofol vs midazolam. Propensity scores were based on age, sex, reason for admission to ICU, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, use of vasoactive medications and use of continuous renal replacement therapy. The cohorts were formed based on 1:1 nearest-neighbor matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score[26]. Sensitivity analyses were based on the full cohort with models adjusted a priori for the same patient characteristics used in the propensity scores. The above analyses were repeated for the 7-category sedation strategy prior to the first ICDSC assessment. For these analyses, we formed six pairwise propensity score-matched cohorts similar to the primary analyses, matching with patients on propofol only for each of the other 6 categories of sedation strategy prior to the first ICDSC assessment. A two-sided p-value < 0.05 was considered statistically significant. Analyses were conducted in R, version 3.5.1.[27] Propensity-score matching was performed using the R package "MatchIt", version 3.0.2. Additionally, to control for the competing effects of delirium and death, a sensitivity analysis of a composite endpoint of delirium or death was calculated.

Results:

There were 2,837 patients in the study cohort (Figure 1), which included 1412 patients (49.8%) receiving a propofol dominant strategy, 356 patients (12.5%) receiving a midazolam dominant strategy and 1069 patients (37.7%) receiving a fentanyl dominant strategy. For those receiving propofol dominant sedation, it was common to receive a

single agent of only propofol (62.8%). While among those receiving fentanyl and midazolam dominant sedation strategies, single agent use was less common with 14.8% and 34.8% only receiving a single agent, respectively." Most patients were male (60.7%) with a median age of 57 (IQR 43-68) years and admitted for a medical reason (50.4%). The median Charlson comorbidity score was 1 (IQR 0-2), admission SOFA score 7 (IQR 4-9) and admission APACHE II score 19 (IQR 14-25). Patients who received a midazolam dominant sedation strategy were more likely admitted for medical reasons (72.8%) and had higher Charlson comorbidity scores, admission SOFA scores and admission APACHE II scores than those receiving propofol and fentanyl dominant sedation strategies. Patients receiving midazolam dominant strategies were also more likely to receive vasoactive medications (68.8%) compared to those predominantly receiving propofol (45.3%) and fentanyl dominant sedation strategies (64.5%). (Table 1).

Due to missing patient characteristics for 5 patients (0.2%), propensity scores were calculated for 1,409 patients receiving propofol dominant strategies, 1,067 patients receiving fentanyl dominant sedation strategies and 356 patients receiving midazolam dominant sedation strategies. Of the patients receiving fentanyl dominant sedation strategies, 201 (18.8%) could not be matched to a patient receiving propofol dominant sedation strategies within the specified caliper width of 0.2; therefore, this resulted in a matched cohort for propofol and fentanyl of 1,732 patients. Of the patients receiving midazolam dominant sedation strategies, all 356 patients could be matched to a patient receiving propofol dominant sedation strategies; therefore, this resulted in a matched cohort for patients with propofol and midazolam dominant sedation strategies of 712 patients. After matching, the baseline characteristics were balanced(Table 1). The median time from admission to first ICDSC in hours were similar between the propofol(median time = 17.1hrs (IQR = 8.5-34.7)), midazolam((median time =17.6 hrs (IQR = 8.8-41.2)) and fentanyl (median time =16.5 hrs (8.8-35.4) dominant strategies. Additionally, the median number of ICDSC assessments per ICU day was similar for propofol(1.4 (IQR =1.0-1.8) , fentanyl(1.4 (IQR 1.0-1.8), midazolam(1.3 (IQR 1.0-1.7) dominant sedation strategies.

In the propensity score-matched cohorts, there was a statistically significant association between delirium and midazolam dominant(odds ratio[OR] 1.46 (95% confidence interval 1.06-2.00); p=0.02) as well as fentanyl dominant (OR 1.22 (95% CI 1.00-1.48); p=0.05) sedation strategies compared to propofol dominant sedation strategies(Figure 2). To control for the effects of death on delirium rates, a sensitivity analysis of the matched cohort was performed using a composite outcome of delirium or death. A statistically significant association between the

composite outcome of delirium and death with midazolam dominant(OR 1.53 (95% CI 1.10-2.12; p=0.011) and fentanyl dominant(OR 1.27 (95% CI 1.04-1.55; p=0.020) strategies was observed, however not for propofol dominant strategies. Sensitivity analyses based on the 7-category sedation strategy prior to the first ICDSC assessment showed an increased odds of delirium for those on more than one agent compared to those on propofol only (Table 2). Among those who ever experienced delirium, the distribution of delirium subtypes was similar between dominant sedation strategies (Table 3). Based on the propensity score-matched cohorts, a fentanyl dominant sedation strategy was associated with longer duration of mechanical ventilation, longer ICU and hospital LOS and more delirium days compared to a propofol dominant sedation strategy, while a midazolam dominant sedation strategy was associated with a longer duration of mechanical ventilation compared to a propofol dominant sedation strategy(Figure 3). Sensitivity analyses of the secondary outcomes and cohort characteristics based on the 7-category sedation strategy can be found in the supplementary results(Supplementary Digital Content - Table 1 & Table 2, respectively). There was a statistically significant association between fentanyl dominant sedation strategy and ICU(OR=1.50 (1.07-2.12)) and 30-day mortality(OR=1.35 (1.02-1.79)) in propensity score-matched analyses(Supplementary Digital Content - Table 3). An additional sensitivity analysis of the same propensity score-matched cohort evaluating sedation strategy dominance for greater than 6 hours can be found in Table 4. This analysis demonstrated a statistically significant association between fentanyl dominant strategies and a composite of delirium or death, ICU mortality, hospital mortality, 30 day mortality, 1 year mortality, hospital length of stay and duration of mechanical ventilation.

Discussion:

Sedative strategies may increase the risk of adverse patient complications such as delirium, or prolonged mechanical ventilation. We found a midazolam dominant sedation strategy was associated with increased risk of developing delirium, duration of mechanical ventilation, and a composite of delirium and death. Alternatively, fentanyl was associated with multiple detrimental outcomes including an increased risk of delirium, a composite outcome of delirium or death, ICU & hospital LOS and duration of mechanical ventilation.

The association between benzodiazepine-based sedation strategies and delirium has been suggested in prior literature [8 17 18]. The importance of these findings should not be understated as patients with delirium suffer prolonged hospital stays, an increased risk of mortality and long term cognitive impairment[7 8]. Sedation using multiple agents was also associated with increased delirium risk, duration of mechanical ventilation, ICU LOS and

hospital LOS. Whether these effects are a direct result from the sedation strategy, the resulting delirium or as a result of other aspects of their critical illness is unclear.

We also re-confirmed the association between midazolam dominant sedation strategies and longer mechanical ventilation but not mortality as reported by Lonardo *et al.*[11]. The mechanism between the association of benzodiazepines and mortality is unclear, however prolonged mechanical ventilation is a known risk factor for mortality[28]. A meta-analysis by Ho *et al.* comparing propofol to other sedation strategies did not demonstrate an impact on mortality; however, it did not specifically look at midazolam compared to other benzodiazpines[29]. The heterogeneity in mortality outcomes may be attributable to variation in sedation depth, as early deep sedation is an independent predictor of delayed time to extubation and long term mortality[12]. Therefore, not only agent choice but also sedation depth might contribute to the variation in mortality risk observed with benzodiazepines.

Sedation with midazolam and fentanyl is often selected for patients with significant hemodynamic instability to avoid the negative ionotropic and vasodilatory effects of propofol. In our study, those receiving midazolam dominant sedation strategies demonstrated significantly higher SOFA scores, APACHE II scores on admission and were more likely to receive vasoactive medications and continuous renal replacement. All of these may impact mortality when unaccounted for and may explain the heterogeneity observed in the literature[30]. For example, Lonardo *et al.* did not control for the presence of renal replacement which has been associated with a high rate of mortality in critically ill patients[11 31]. Our use of detailed clinical data for risk adjustment may help explain the differences in mortality compared to prior reports.

A fentanyl dominant sedation strategy was significantly associated with an increased risk of delirium, a composite of delirium or death, ICU LOS, hospital LOS and duration of mechanical ventilation. Prior literature shows associations with delayed extubation when given in the first 48 hours, which supports our findings[12]. What is unclear is whether our result is a direct effect of fentanyl, an indirect effect from resulting complications of fentanyl use, for example a pulmonary embolism or pneumonia, or simply an observed association driven by an unidentified confounder. Fentanyl dominant strategies were associated with increased risk of ICU mortality, 30-day mortality, and at hospital discharge but not 1 year. It is difficult to know what to make of these observations. The relationship between fentanyl use and ICU mortality has been incompletely explored in the literature. The mortality risk associated with fentanyl use may be attributable to prolongations in mechanical ventilation[28]. In our data, the effect of mortality appeared strongest in those receiving only fentanyl and was less robust when used in combination.

However, when fentanyl was the dominant strategy for greater than 6 hours compared to the other two strategies, the association between fentanyl and negative patient centred outcomes was more consistent. This may suggest the detrimental association between fentanyl dominant strategies and patient centred outcomes observed is time dependent. Another possibility could be the immunomodulatory effects of narcotics. The mu-opioid receptor is expressed on macrophages and T-lymphocytes, and chronic administration may increase the risk of bacterial infection[32-34]. Therefore, large doses of fentanyl may contribute to further immune dysregulation thereby placing critically ill patients at risk of infection. A final possibility is the use of fentanyl in the provision of palliative symptom control, therefore the mortality association is a marker of this practice. Further study is required to better delineate the true nature of the association between fentanyl and deleterious patient outcomes in the ICU.

Our studies strength is our large cohort size supported by granular patient detail extracted from a prospectively collected, clinical database representing multiple ICUs and the covariates were rigorously controlled using a propensity matched model[22]. The multicenter study design provides a pragmatic view of how sedation strategies are utilized in clinical practice. Limitations of our study include the possibility of confounding bias due to unmeasured impactful covariates or confounding by indication. Patients receiving midazolam dominant strategies were clearly more critically ill compared to those receiving propofol dominant strategies manifest by higher APACHE II scores, greater vasopressor requirements, and higher rates of renal replacement. To compensate, we conducted propensity score-matched analyses adjusted for known covariates. Additionally, fentanyl and midazolam are often used concurrently. Clearly teasing apart the isolated effects of each medication may be challenging. Adjustment with our statistical model should minimize this effect, however, it is possible that unrecognized confounders which are not accounted for in the model could introduce unrecognized bias. Randomized controlled trials would better assess this limitation. Moreover, we focused primarily on the presence or absence of continuous infusions and did not quantify the impact of independent drug boluses. However, this effect would lessen the association with our primary outcome suggesting our observed associations are conservative. Another limitation is the use of drug duration as a surrogate for the impact of the sedation strategy rather than in vivo plasma concentrations. Patient factors may impact midazolam metabolism due to differences in age, hepatic or renal dysfunction or co-administration of medications with similar metabolic pathways[35-37]. Finally, the definition of dominant sedation strategy based on longest duration of infusion prior to first ICDSC may be considered arbitrary. It is also possible that the current definition classifies some patients as having one dominant sedation strategy when

multiple infusions were discontinued in a noticeably short time frame. However, defining sedation in the setting of multiple agents has been incompletely explored in the literature, therefore novel definitions are required. Our data closely reflects multiple findings previously reported with both midazolam and fentanyl sedation. Furthermore, when restricted to patients who received a dominant sedation strategy for greater than 6 hours, the association between fentanyl dominant strategies and negative patient outcomes was more apparent. This reduces the possibility our findings are pure chance.

Conclusion:

This multi-center, propensity score-matched cohort study demonstrates a novel association between fentanyl dominant sedation strategies and negative outcomes in the ICU. Fentanyl dominant sedation strategies were associated with an increased risk of delirium, a composite of delirium or death, duration of ventilation, ICU LOS and hospital LOS. We also confirmed previous reports including an increased risk of delirium and duration of mechanical ventilation with midazolam dominant sedation strategies. This study highlights the need for additional research to further evaluate potentially negative effects of fentanyl and midazolam based sedation strategies.

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to the methods section of the manuscript. Drs KF, DN, TS, PC were involved in developing the concept, study protocol, study oversight and contributed to the discussion of the manuscript.

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Tables:

Table 1: Baseline Characteristics

	Overall cohort			**Dominant sedation strategy matched cohorts**			
				Propofol vs. Midazolam matched cohort		Propofol vs. Fentanyl matched cohort	
	Propofol (n=1412)	Fentanyl (n=1069)	Midazolam (n=356)	Propofol (n=356)	Midazolam (n=356)	Propofol (n=866)	Fentanyl (n=866)
Characteristic							
Age, median (IQR)	56 (42-67)	59 (44-69)	59 (46-71)	58 (48-69)	59 (46-71)	57 (46-68)	57 (42-69)
Male, n (%)	843 (59.7)	656 (61.4)	223 (62.6)	227 (63.8)	223 (62.6)	533 (61.5)	520 (60.0)
Admission reason, n (%)							
Medical	791 (56.0)	379 (35.5)	259 (72.8)	253 (71.1)	259 (72.8)	426 (49.2)	379 (43.8)
Surgical	265 (18.8)	405 (37.9)	69 (19.4)	74 (20.8)	69 (19.4)	256 (29.6)	248 (28.6)

Neurological	245 (17.4)	73 (6.8)	19 (5.3)	18 (5.1)	19 (5.3)	76 (8.8)	73 (8.4)
Trauma	109 (7.7)	211 (19.7)	9 (2.5)	11 (3.1)	9 (2.5)	108 (12.5)	166 (19.2)
Location admitted from							
Emergency Room	833 (59.0%)	413 (38.6%)	190 (53.4%)	202 (56.7)	190 (53.4)	441 (50.9)	369 (42.6)
Operating Room/Recovery	278 (19.7%)	399 (37.3%)	59 (16.6%)	63 (17.7)	59 (16.6)	232 (26.8)	271 (31.3)
Hospital Ward	254 (18.0%)	209 (19.6%)	91 (25.6%)	85 (23.9)	91 (25.6)	165 (19.1)	180 (20.8)
Another Hospital	26 (1.8%)	24 (2.2%)	7 (2.0%)	4 (1.1)	7 (2.0)	17 (2.0)	23 (2.7)
Other	21 (1.5%)	24 (2.2%)	9 (2.5%)	2 (0.6)	9 (2.5)	11 (1.3)	23 (2.7)
Charlson score, n (%)							
0	582 (41.2%)	422 (39.5%)	121 (34.0%)	127 (35.7)	121 (34.0)	322 (37.2)	336 (38.8)
1	317 (22.5%)	239 (22.4%)	70 (19.7%)	61 (17.1)	70 (19.7)	201 (23.2)	207 (23.9)
2+	513 (36.3%)	408 (38.2%)	165 (46.3%)	168 (47.2)	165 (46.3)	343 (39.6)	323 (37.3)
Charlson score, median (IQR)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-2)
Admission SOFA score, median (IQR)	6 (4-8)	7 (5-10)	8 (6-11)	8 (5-10)	8 (6-11)	7 (4-9)	7 (4-10)
Admission APACHE II score, median (IQR)	18 (13-24)	19 (14-25)	23 (16-28)	21 (16-27)	23 (16-28)	19 (14-24)	19 (13-26)
Vasoactive medications, n (%)	639 (45.3%)	690 (64.5%)	245 (68.8%)	241 (67.7)	245 (68.8)	526 (60.7)	488 (56.4)
Continuous renal replacement therapy, n (%)	59 (4.2%)	78 (7.3%)	33 (9.3%)	28 (7.9)	33 (9.3)	52 (6.0)	73 (8.4)

Table 2: Sensitivity Analyses examining the relationship between delirium and individual sedation agents prior to first ICDSC assessment

	Overall Cohort			**Matched cohorts**			
Sedation agent prior to first ICDSC assessment	**Number of patients**	**Ever Delirium, n (%)**	**Adjusted OR (95% CI)[1]**	**Number of patients per group**	**Ever Delirium for propofol patients from matched cohorts, n (%)**	**Ever Delirium, n (%)**	**Propensity score-matched OR for Ever delirium(95% CI)[2]**
Propofol	887	509 (57.4)	1.00 (reference group)	N/A[3]	N/A[3]	N/A[3]	1.00 (reference group)
Fentanyl	158	91 (57.6)	1.04 (0.71-1.52)	152	74 (48.7)	87 (57.2)	1.41 (0.90-2.22)
Midazolam	124	77 (62.1)	1.11 (0.73-1.69)	122	69 (56.6)	75 (61.5)	1.23 (0.74-2.05)
Propofol + Fentanyl	854	543 (63.6)	1.32 (1.06-1.65)	565	323 (57.2)	347 (61.4)	1.19 (0.94-1.51)

Propofol + Midazolam	224	163 (72.8)	1.72 (1.23-2.43)	223	143 (64.1)	162 (72.6)	1.49 (1.00-2.23)
Fentanyl + Midazolam	222	160 (72.1)	1.72 (1.22-2.46)	214	119 (55.6)	153 (71.5)	2.00 (1.34-3.00)
All 3	368	269 (73.1)	1.84 (1.38-2.47)	335	199 (59.4)	241 (71.9)	1.75 (1.27-2.42)

Table 3: Delirium subtype by dominant sedation strategy prior to first ICDSC assessment among patients experiencing delirium for the propensity score-matched cohorts

	Dominant sedation strategy			
	Propofol vs. Fentanyl matched cohort patients experiencing delirium		Propofol vs. Midazolam matched cohort patients experiencing delirium	
Delirium Subtype	Propofol (n=529)	Fentanyl (n=569)	Propofol (n=228)	Midazolam (n=257)
Hyperactive only, n (%)	47 (8.9)	40 (7.0)	15 (6.6)	25 (9.7)
Hypoactive only, n (%)	210 (39.7)	228 (40.1)	104 (45.6)	106 (41.2)
Mixed, n (%)	254 (48.0)	289 (50.8)	103 (45.2)	123 (47.9)
Unable to assess or classify, n (%)	18 (3.4)	12 (2.1)	6 (2.6)	3 (1.2)

Table 4: Sensitivity analyses based on those on a single sedation strategy or those whose sedation strategy was dominant for ≥6 hours over the other 2 strategies.

Outcome	**Dominant Sedation Strategy**	**Propensity score-matched odds ratio, mean ratio or rate ratio (95% CI)[1]**
Delirium ever	Propofol	1.00 (reference group)
	Fentanyl	1.29 (0.99-1.69)
	Midazolam	**1.64 (1.12-2.41)**
Delirium or ICU death	Propofol	1.00 (reference group)
	Fentanyl	**1.38 (1.05-1.81)**
	Midazolam	**1.75 (1.18-2.60)**
ICU Mortality	Propofol	1.00 (reference group)
	Fentanyl	**1.82 (1.18-2.84)**
	Midazolam	1.31 (0.73-2.39)
Hospital Mortality	Propofol	1.00 (reference group)
	Fentanyl	**1.69 (1.19-2.42)**
	Midazolam	1.50 (0.92-2.49)
Died within 30 days of ICU admission	Propofol	1.00 (reference group)
	Fentanyl	**1.84 (1.27-2.68)**
	Midazolam	1.14 (0.69-1.89)
Died within 1 year of ICU admission	Propofol	1.00 (reference group)
	Fentanyl	**1.38 (1.02-1.86)**
	Midazolam	1.16 (0.77-1.76)
Died within 1.5 years of ICU admission	Propofol	1.00 (reference group)
	Fentanyl	1.25 (0.94-1.66)
	Midazolam	1.25 (0.84-1.85)
ICU length of stay, mean ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl	**1.23 (1.09-1.39)**
	Midazolam	1.01 (0.86-1.20)
Hospital length of stay, mean ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl	**1.31 (1.13-1.51)**
	Midazolam	1.01 (0.83-1.22)
Duration of invasive ventilation, mean	Propofol	1.00 (reference group)

ratio (95% CI)	Fentanyl	**1.35 (1.14-1.59)**
	Midazolam	1.17 (0.94-1.46)
Number of delirium days, rate ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl	1.19 (0.99-1.43)
	Midazolam	1.11 (0.85-1.44)

[1]Data presented as odds ratios unless otherwise indicated

Figure Legends:

Figure 1: Cohort diagram

Figure 2: Propensity score-matched odds ratios of delirium by dominant sedation strategy prior to first ICDSC assessment

Figure 3: Forest plot of propensity score-matched mean or rate ratios of secondary outcomes and sedation strategy

Figure 1: Cohort diagram

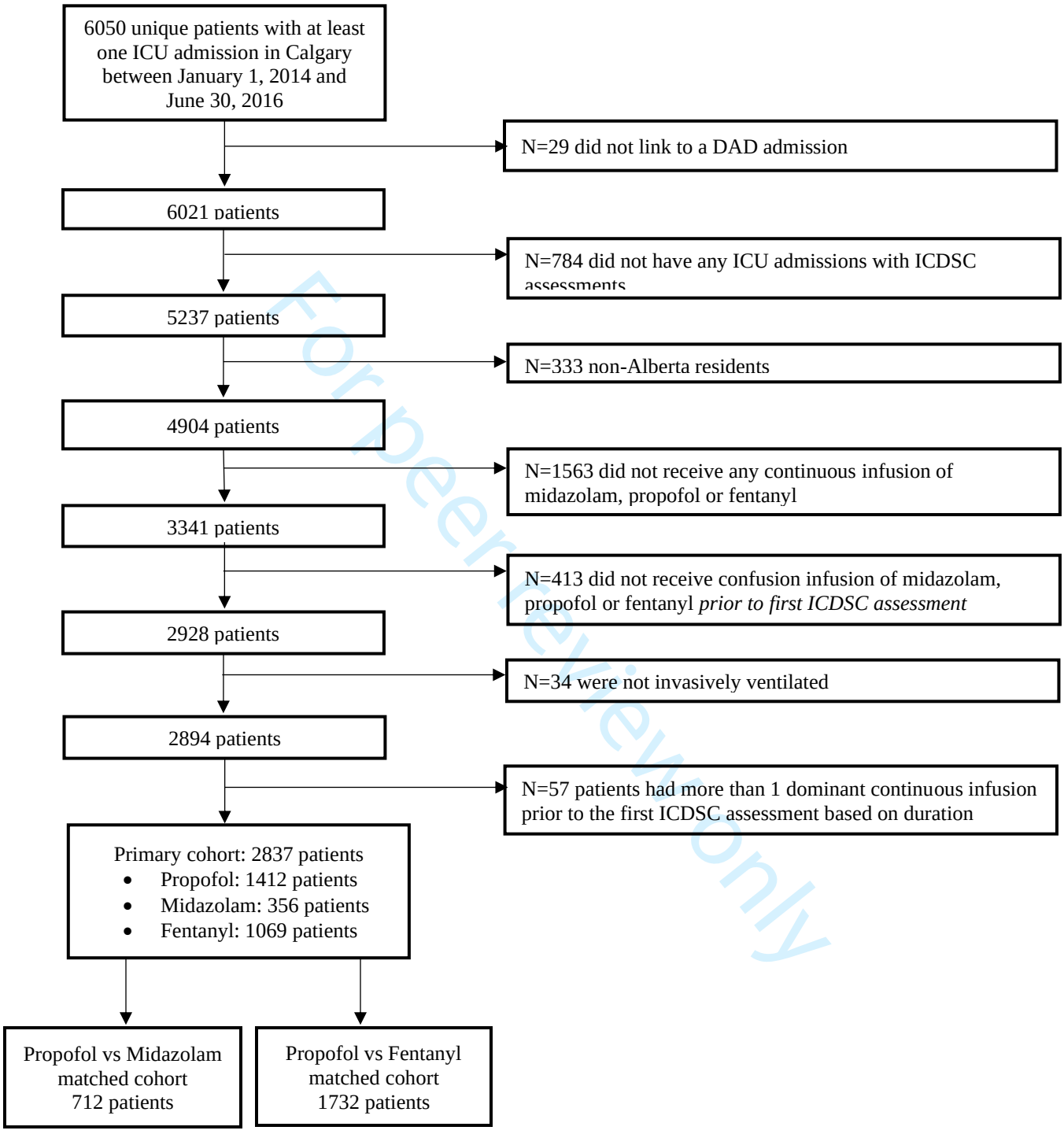

Figure 2: Propensity score-matched odds ratios of delirium by dominant sedation strategy prior to first ICDSC assessment

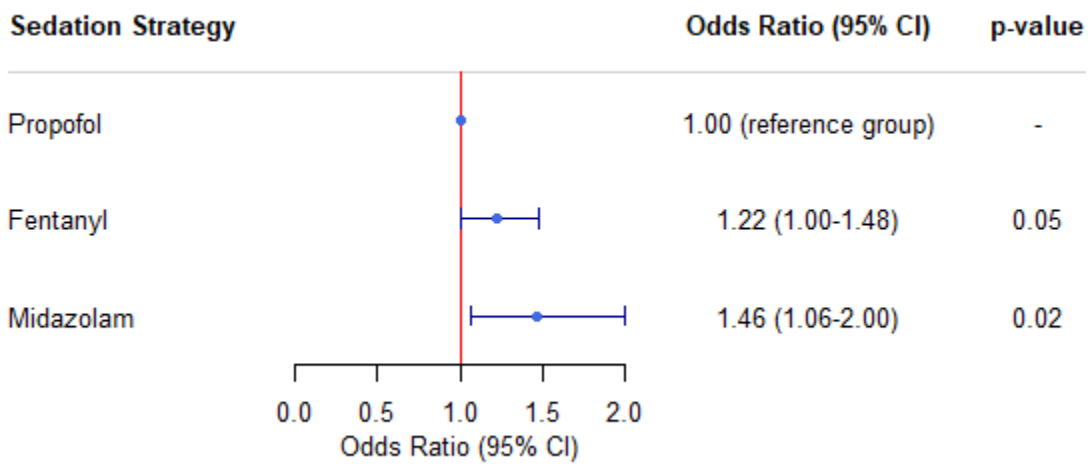

Figure 3: Forest plot of propensity score-matched mean or rate ratios of secondary outcomes and sedation strategy

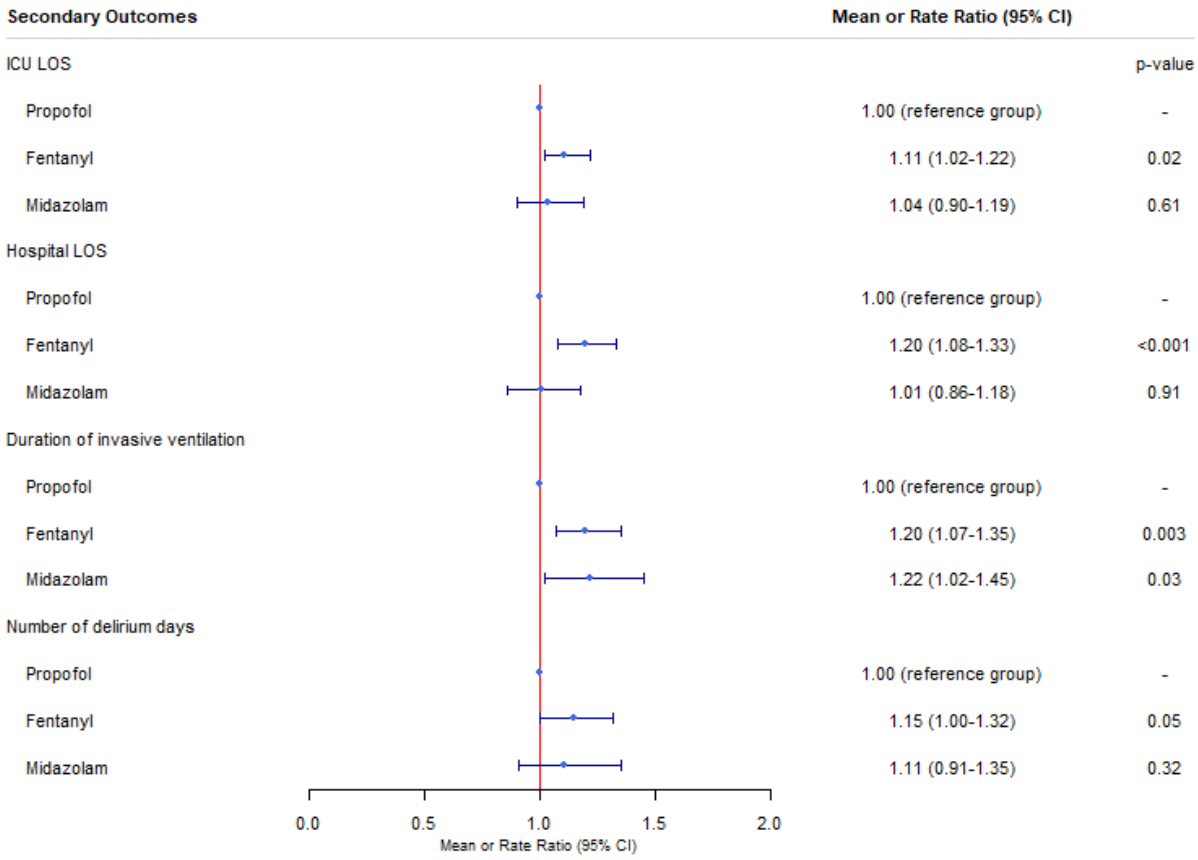

Table S1: Secondary outcomes by sedation strategy prior to first ICDSC assessment

Propensity score-matched mean ratio or rate ratio (95% CI)[1]	**ICU LOS**	**Hospital LOS**	**Duration of invasive ventilation**	**Number of delirium days**
Sedation prior to first ICDSC assessment				
Propofol	1.00 (reference group)	1.00 (reference group)	1.00 (reference group)	1.00 (reference group)
Fentanyl	1.06 (0.85-1.33)	1.25 (0.97-1.61)	1.00 (0.74-1.35)	1.03 (0.69-1.55)
Midazolam	0.83 (0.65-1.06)	0.98 (0.75-1.28)	1.00 (0.73-1.38)	0.88 (0.59-1.31)
Propofol + Fentanyl	**1.17 (1.05-1.30)**	**1.20 (1.05-1.38)**	**1.37 (1.18-1.58)**	1.08 (0.90-1.31)
Propofol + Midazolam	1.16 (0.99-1.36)	0.86 (0.68-1.08)	**1.59 (1.28-1.99)**	1.11 (0.87-1.41)
Fentanyl + Midazolam	**1.40 (1.17-1.67)**	**1.27 (1.02-1.57)**	**1.95 (1.54-2.46)**	1.28 (0.97-1.69)
All 3	**1.73 (1.52-1.98)**	**1.39 (1.18-1.63)**	**2.47 (2.06-2.97)**	**1.35 (1.10-1.67)**

[1]Propensity score based on age, sex, admission class, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, vasoactive medications, continuous renal replacement therapy. 1:1 nearest-neighbor matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score

Table S2: Propensity score matched models of the relationship between mortality outcomes and dominant sedation strategy prior to first ICDSC assessment

Outcome	Dominant Sedation Strategy	Mortality, n (%)	Propensity score-matched OR (95% CI)[2]
ICU Mortality	Propofol	94 (6.7)	1.00 (reference)
	Fentanyl	104 (9.7)	**1.50 (1.07-2.12)**
	Midazolam	39 (11.0)	1.20 (0.74-1.97)
Hospital Mortality	Propofol	157 (11.1)	1.00 (reference)
	Fentanyl	166 (15.5)	1.27 (0.97-1.67)
	Midazolam	59 (16.6)	1.14 (0.76-1.70)
Died within 30 days of ICU admission	Propofol	148 (10.5)	1.00 (reference)
	Fentanyl	148 (13.8)	**1.35 (1.02-1.79)**
	Midazolam	50 (14.0)	1.02 (0.67-1.57)
Died within 1 year of ICU admission	Propofol	268 (19.0)	1.00 (reference)
	Fentanyl	248 (23.2)	1.13 (0.90-1.43)
	Midazolam	91 (25.6)	1.01 (0.72-1.42)

Supplementary Table 3: Table of baseline characteristics for sensitivity analyses

	Propofol (n=887)	Fentanyl (n=158)	Midazolam (n=124)	Propofol + Fentanyl (n=854)	Propofol + Midazolam (n=224)	Fentanyl + Midazolam (n=222)	All 3 (n=368)
Characteristic							
Age, median (IQR)	58 (46-69)	64 (54-74)	66 (54-74)	55 (40-67)	51 (35-60)	61 (51-71)	52 (40-65)
Male, n (%)	506 (57.0)	79 (50.0)	79 (63.7)	532 (62.3)	145 (64.7)	133 (59.9)	248 (67.4)
Admission reason, n (%)							
Medical	518 (58.5)	59 (37.3)	87 (70.2)	236 (27.7)	176 (78.6)	121 (54.5)	232 (63.0)
Surgical	163 (18.4)	72 (45.6)	30 (24.2)	299 (35.1)	7 (3.1)	81 (36.5)	87 (23.6)
Neurological	169 (19.1)	10 (6.3)	6 (4.8)	102 (12.0)	37 (16.5)	3 (1.4)	10 (2.7)
Trauma	35 (4.0)	17 (10.8)	1 (0.8)	216 (25.3)	4 (1.8)	17 (7.7)	39 (10.6)
Location admitted from							
Emergency Room	520 (58.6)	53 (33.5)	49 (39.5)	367 (43.0)	168 (75.0)	93 (41.9)	186 (50.5)
Operating Room/Recovery	170 (19.2)	62 (39.2)	27 (21.8)	320 (37.5)	6 (2.7)	65 (29.3)	86 (23.4)
Hospital Ward	166 (18.7)	39 (24.7)	43 (34.7)	140 (16.4)	40 (17.9)	49 (22.1)	77 (20.9)
Another Hospital	17 (1.9)	3 (1.9)	2 (1.6)	13 (1.5)	7 (3.1)	7 (3.2)	8 (2.2)
Other	14 (1.6)	1 (0.6)	3 (2.4)	14 (1.6)	3 (1.3)	8 (3.6)	11 (3.0)
Charlson score, n (%)							
0	338 (38.1)	47 (29.7)	30 (24.2)	387 (45.3)	106 (47.3)	74 (33.3)	143 (38.9)
1	204 (23.0)	35 (22.2)	19 (15.3)	171 (20.0)	55 (24.6)	50 (22.5)	92 (25.0)
2+	345 (38.9)	76 (48.1)	75 (60.5)	296 (34.7)	63 (28.1)	98 (44.1)	133 (36.1)

Charlson score, median (IQR)	1 (0-3)	1 (0-3)	2 (1-4)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-2)
Admission SOFA score, median (IQR)	6 (4-8)	8 (5-10)	8 (5-10)	6 (4-9)	7 (5-9)	9 (6-11)	8 (5-11)
Admission APACHE II score, median (IQR)	18 (14-23)	20 (15-26)	23 (16-28)	17 (12-22)	20 914-25)	22 (16-29)	21 (14-26)
Vasoactive medications, n (%)	356 (40.1)	105 (66.5)	81 (65.3)	477 (55.9)	117 (52.2)	175 (78.8)	263 (71.5)
Continuous renal replacement therapy, n (%)	35 (3.9)	10 (6.3)	9 (7.3)	41 (4.8)	7 (3.1)	32 (14.4)	36 (9.8)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, 6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6, Supplement methods
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	4, 7 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	7 Table 2, 3,

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2,3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Sedation strategy and ICU Delirium: A multi-center, population-based propensity score-matched cohort study

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Figures: 3

Conflicts of Interest: No author has a conflict of interest to declare.

Keywords: Delirium, ICU sedation, fentanyl sedation, midazolam sedation

Objectives: We examined the relationship between dominant sedation strategy, risk of delirium, and patient-centered outcomes in adults admitted to intensive care units(ICUs).

Design: Retrospective propensity-matched cohort study.

Setting: Mechanically-ventilated adults (≥ 18 years) admitted to four Canadian hospital medical/surgical ICUs from 2014 – 2016 in Calgary, Alberta, Canada.

Participants: 2837 mechanically-ventilated adults (≥ 18 years) requiring admission to a medical/surgical ICU were evaluated for the relationship between sedation strategy and delirium.

Interventions: None.

Primary and secondary outcome measures: The primary exposure was dominant sedation strategy, defined as the sedative infusion, including midazolam, propofol or fentanyl, with the longest duration before the first delirium assessment. The primary outcome was 'ever delirium' identified using the Intensive Care Delirium Screening Checklist (ICDSC). Secondary outcomes included mortality, length of stay (LOS), duration of ventilation, and number of days with delirium. We analyzed the cohort with two propensity score (patient characteristics and therapies received) matched cohorts (propofol vs. fentanyl and propofol vs. midazolam).

Results: 2,837 patients (60.7% male; median age 57 years (interquartile range 43-68)) were considered for propensity matching. In propensity score-matched cohorts(propofol vs. midazolam, n=712; propofol vs. fentanyl, n=1,732), the odds of delirium were significantly higher with midazolam (odds ratio (OR) 1.46 (95% confidence interval(CI) 1.06-2.00)) and fentanyl (OR 1.22 (95% CI 1.00-1.48)) compared to propofol dominant sedation strategies. Dominant sedation strategy with midazolam and fentanyl were associated with a longer duration of ventilation compared to propofol. Fentanyl was also associated with increased ICU mortality(OR 1.50 (1.07-2.12)) ICU and hospital LOS compared to a propofol dominant sedation strategy.

Conclusions: We identified a novel association between fentanyl dominant sedation strategies and an increased risk of delirium, a composite outcome of delirium or death, duration of mechanical ventilation, ICU LOS, and hospital LOS. Midazolam dominant sedation strategies were also associated with increased delirium risk and duration of mechanical ventilation.

Article Summary:

- We examine the effects of midazolam and fentanyl sedation strategies on delirium and patient-centered outcomes using a large cohort of general intensive care patients.
- To reduce bias, we used a propensity score matching process on a extensive database.
- One fundamental limitation is secondary to the concurrent use of multiple overlapping sedation strategies, which may impact the results.
- Based on the limitations and the nature of cohort studies, this study as hypothesis-generating.

Introduction:

Delirium in critically ill patients is an acute confusional state marked by severe disorganization of cognition, fluctuating course, attentional deficit, and a disturbance of awareness[1]. Older age, severity of illness, presence of mechanical ventilation, coma, and sedative medications place over 50% of ICU patients at risk for developing delirium[2-6]. Delirium in the ICU is common and may prolong hospital stay, increase mortality risk and contribute to long-term cognitive impairment[7 8]. With a burgeoning elderly population, ICU admission requiring mechanical ventilation is estimated to increase by 80% by 2026; therefore understanding potential contributors to delirium is paramount[9 10].

Over-sedation in the ICU, with benzodiazepines, in particular, may be harmful[11,12]. Prospective cohort and randomized controlled trials support shorter durations of mechanical ventilation, more rapid awakening with propofol or dexmedetomidine than midazolam [13-17]. Similarly, a population-based study by Lonardo *et al.* demonstrated higher mortality, longer duration of mechanical ventilation, and longer ICU length of stay (LOS) in patients managed with benzodiazepines compared to propofol[11]. Lonardo *et al.* postulated midazolam's mortality effect might be due to increased rates of delirium. Delirium is associated with mortality, and some evidence supports patients treated with benzodiazepines may demonstrate higher rates of delirium in the ICU[8 13 18 19]. However, the association between benzodiazepines and delirium is inconsistent[6].

Sedation strategies often employ both a sedative, like propofol, and an analgesic, like fentanyl, simultaneously to achieve the desired effect. However, studies evaluating the clinical effects of these sedation strategies are lacking. Additional research is necessary to understand the effects of sedation strategies on delirium, hospital length of stay (LOS), and survival outcomes. Our study examined the relationship between dominant sedation strategy (continuously infused propofol, fentanyl, and/or midazolam), delirium, and important patient-centered outcomes, in a multi-center population-based sample of mechanically-ventilated adults admitted to ICU.

Methods:

Ethics Approval Statement:

This retrospective cohort study was reported in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[20] and approved by the conjoint health research ethics board at the University of Calgary (REB17-0389).

Patient & Public Involvement Statement:

Neither patients, nor the public were not involved in the design, collection, compilation or completion of this research study.

Study Setting & Population:

We identified consecutive mechanical ventilated adults (≥ 18 years) admitted to four medical-surgical ICUs in Calgary, Alberta, Canada between January 1, 2014, to June 30th, 2016. Patients were excluded if:

1) Their ICU electronic health data did not link to an appropriate inpatient (hospital) admission
2) They did not have any ICU admissions with at least 1 Intensive Care Delirium Screening Checklist (ICDSC) assessment (details described in the *Outcome Measures* section)
3) They were non-Alberta residents (to allow for mortality outcome follow-up post hospital discharge)
4) They did not receive at least 1 continuous infusion of midazolam, propofol or fentanyl prior to the first ICDSC assessment.
5) They were never invasively ventilated during their ICU stay.
6) They did not have a single dominant continuous infusion prior to the first ICDSC assessment (see definition of dominant sedation strategy in the *Exposure Measure* section below for further detail).

If the patient was readmitted to ICU more than once during the study period, then only the first admission with at least 1 ICDSC assessment was used. The ICUs are staffed by accredited intensive care physicians which provide mechanical ventilation, vasoactive medications, and invasive monitoring.

Data sources:

Study data was derived from three electronic databases[21-23]. eCritical Alberta, a database and electronic medical record, that prospectively captures detailed clinical and demographic information[22]. The discharge abstract database (DAD) captures data on all hospitalized patients, including admission date, discharge, survival status, and up to 25 diagnostic codes from the International Classification of Diseases, 10th revision, Canadian enhancement. Out of hospital deaths were obtained from Alberta Vital Statistics, which captures all deaths occurring in Alberta. Data from Alberta Vital Statistics was available up to December 30, 2017, which provided at least 18 months of follow-up from the ICU admission date.

Exposures and Definitions:

The main study exposure was dominant sedation strategy prior to the first ICDSC assessment. A sedation strategy was defined as a continuous analgo-sedative infusion limited to midazolam, fentanyl, and propofol.

Infusions were selected based on a screening survey which demonstrated small populations utilizing alternative sedation strategies. There were seven possible combinations for the sedation strategy prior to the first ICDSC assessment: 1) propofol only, 2) fentanyl only, 3) midazolam only, 4) propofol and fentanyl, 5) propofol and midazolam, 6) fentanyl and midazolam, and 7) all three agents. A high number of patients received more than 1 agent, therefore we classified patients into a dominant sedation strategy, defined as the longest continuous duration of infusion prior to the first ICDSC assessment, which consists of three categories for the primary analyses. For example, if fentanyl was provided for the longest duration, fentanyl was considered the dominant sedation strategy. It is possible the patient could have received propofol or midazolam (or neither) for a duration less than fentanyl. If the patient received two agents for the same duration, the patient was excluded as no strategy was dominant. As sensitivity analyses, all seven possible combinations of the sedation strategy used prior to the first ICDSC assessment were considered.

Outcome Measures:

The primary outcome was categorized as 'ever/never delirium' during ICU admission compatible with previously established delirium outcome measures[7]. All ICU patients with a Richmond Agitation Sedation Scale(RASS)[24] score ≥-3 were evaluated twice daily using the ICDSC tool[25] and received a protocolized sedation awakening trial. The ICDSC is a validated delirium assessment tool[25]. Ever delirium patients were those with an *ICDSC score* ≥4; never delirium were those with an *ICDSC score* <4. Total number of days with an *ICDSC score* ≥4 defined delirium duration. Duration of delirium (days) was examined in secondary analyses.

Delirium motor subtypes were identified using the RASS, based on previously published criteria[18], and associated positive ICDSC score of ≥4. The scale is scored from -5 points (unarousable) to 0 points (calm) to +4 points (combative), where scores between -3 to 0 indicate hypoactive delirium, scores between 1 to 3 indicate hyperactive delirium, and scores that fluctuate between hypoactive and hyperactive indicate mixed delirium. All ICDSC scores ≥4 were linked to the closest RASS score within 4 hours of charting. If there was no RASS score documented within 4 hours of the ICDSC score, the sub-type was considered "unable to be classified". If there was a RASS score within 4 hours of the ICDSC score but the RASS was -5, -4 or +4, the sub-type was considered "unable to be assessed". If at least 1 assessment indicated hypoactive delirium and at least 1 assessment indicated hyperactive delirium the sub-type was considered mixed for that specific patient.

Secondary outcomes were mortality in the ICU and hospital, duration of mechanical ventilation, and ICU & hospital lengths of stay (LOS). Patient mortality was also reported at 30-days and 1-year. Duration of invasive mechanical ventilation was defined as the time a patient required the use of invasive ventilator.

Statistical Analysis:

Baseline characteristics were summarized using median with interquartile range (IQR) and frequency with percent and compared between sedation strategies using chi-squared tests and Kruskal-Wallis rank sum tests, as appropriate. For the primary outcome analysis, logistic regression was used to assess the association between dominant sedation strategy (propofol vs midazolam vs fentanyl) and risk of developing delirium. The relationship between dominant sedation strategy and delirium duration was analyzed using negative binomial models. The relationship between dominant sedation strategy and mortality outcomes were analyzed using logistic regression models. The relationship between dominant sedation strategy and LOS outcomes (ICU and hospital) were analyzed using linear regression models with a log-transformation of ICU LOS and hospital LOS. Primary analyses for all outcomes were based on forming two propensity score-matched cohorts: 1) propofol vs fentanyl and 2) propofol vs midazolam. Propensity scores were based on age, sex, reason for admission to ICU, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, use of vasoactive medications and use of continuous renal replacement therapy. The cohorts were formed based on 1:1 nearest-neighbor matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score[26]. Sensitivity analyses were based on the full cohort with models adjusted a priori for the same patient characteristics used in the propensity scores. The above analyses were repeated for the 7-category sedation strategy prior to the first ICDSC assessment. For these analyses, we formed six pairwise propensity score-matched cohorts similar to the primary analyses, matching with patients on propofol only for each of the other 6 categories of sedation strategy prior to the first ICDSC assessment. A two-sided p-value < 0.05 was considered statistically significant. Analyses were conducted in R, version 3.5.1.[27] Propensity-score matching was performed using the R package "MatchIt", version 3.0.2. Additionally, to control for the competing effects of delirium and death, a sensitivity analysis of a composite endpoint of delirium or death was calculated.

Results:

There were 2,837 patients in the study cohort (Figure 1), which included 1412 patients (49.8%) receiving a propofol dominant strategy, 356 patients (12.5%) receiving a midazolam dominant strategy and 1069 patients (37.7%) receiving a fentanyl dominant strategy. For those receiving propofol dominant sedation, it was common to receive a

single agent of only propofol (62.8%). While among those receiving fentanyl and midazolam dominant sedation strategies, single agent use was less common with 14.8% and 34.8% only receiving a single agent, respectively." Most patients were male (60.7%) with a median age of 57 (IQR 43-68) years and admitted for a medical reason (50.4%). The median Charlson comorbidity score was 1 (IQR 0-2), admission SOFA score 7 (IQR 4-9) and admission APACHE II score 19 (IQR 14-25). Patients who received a midazolam dominant sedation strategy were more likely admitted for medical reasons (72.8%) and had higher Charlson comorbidity scores, admission SOFA scores and admission APACHE II scores than those receiving propofol and fentanyl dominant sedation strategies. Patients receiving midazolam dominant strategies were also more likely to receive vasoactive medications (68.8%) compared to those predominantly receiving propofol (45.3%) and fentanyl dominant sedation strategies (64.5%). (Table 1).

Due to missing patient characteristics for 5 patients (0.2%), propensity scores were calculated for 1,409 patients receiving propofol dominant strategies, 1,067 patients receiving fentanyl dominant sedation strategies and 356 patients receiving midazolam dominant sedation strategies. Of the patients receiving fentanyl dominant sedation strategies, 201 (18.8%) could not be matched to a patient receiving propofol dominant sedation strategies within the specified caliper width of 0.2; therefore, this resulted in a matched cohort for propofol and fentanyl of 1,732 patients. Of the patients receiving midazolam dominant sedation strategies, all 356 patients could be matched to a patient receiving propofol dominant sedation strategies; therefore, this resulted in a matched cohort for patients with propofol and midazolam dominant sedation strategies of 712 patients. After matching, the baseline characteristics were balanced(Table 1). The median time from admission to first ICDSC in hours were similar between the propofol(median time = 17.1hrs (IQR = 8.5-34.7)), midazolam((median time =17.6 hrs (IQR = 8.8-41.2)) and fentanyl (median time =16.5 hrs (8.8-35.4) dominant strategies. Additionally, the median number of ICDSC assessments per ICU day was similar for propofol(1.4 (IQR =1.0-1.8) , fentanyl(1.4 (IQR 1.0-1.8), midazolam(1.3 (IQR 1.0-1.7) dominant sedation strategies.

In the propensity score-matched cohorts, there was a statistically significant association between delirium and midazolam dominant(odds ratio[OR] 1.46 (95% confidence interval 1.06-2.00); p=0.02) as well as fentanyl dominant (OR 1.22 (95% CI 1.00-1.48); p=0.05) sedation strategies compared to propofol dominant sedation strategies(Figure 2). To control for the effects of death on delirium rates, a sensitivity analysis of the matched cohort was performed using a composite outcome of delirium or death. A statistically significant association between the

composite outcome of delirium and death with midazolam dominant(OR 1.53 (95% CI 1.10-2.12; p=0.011) and fentanyl dominant(OR 1.27 (95% CI 1.04-1.55; p=0.020) strategies was observed, however not for propofol dominant strategies. Sensitivity analyses based on the 7-category sedation strategy prior to the first ICDSC assessment showed an increased odds of delirium for those on more than one agent compared to those on propofol only (Table 2). Among those who ever experienced delirium, the distribution of delirium subtypes was similar between dominant sedation strategies (Table 3). Based on the propensity score-matched cohorts, a fentanyl dominant sedation strategy was associated with longer duration of mechanical ventilation, longer ICU and hospital LOS and more delirium days compared to a propofol dominant sedation strategy, while a midazolam dominant sedation strategy was associated with a longer duration of mechanical ventilation compared to a propofol dominant sedation strategy(Figure 3). Sensitivity analyses of the secondary outcomes and cohort characteristics based on the 7-category sedation strategy can be found in the supplementary results(Supplementary Digital Content - Table 1 & Table 2, respectively). There was a statistically significant association between fentanyl dominant sedation strategy and ICU(OR=1.50 (1.07-2.12)) and 30-day mortality(OR=1.35 (1.02-1.79)) in propensity score-matched analyses(Supplementary Digital Content - Table 3). An additional sensitivity analysis of the same propensity score-matched cohort evaluating sedation strategy dominance for greater than 6 hours can be found in Table 4. This analysis demonstrated a statistically significant association between fentanyl dominant strategies and a composite of delirium or death, ICU mortality, hospital mortality, 30 day mortality, 1 year mortality, hospital length of stay and duration of mechanical ventilation.

Discussion:

Sedative strategies may increase the risk of adverse patient complications such as delirium, or prolonged mechanical ventilation. We found a midazolam dominant sedation strategy was associated with increased risk of developing delirium, duration of mechanical ventilation, and a composite of delirium and death. Alternatively, fentanyl was associated with multiple detrimental outcomes including an increased risk of delirium, a composite outcome of delirium or death, ICU & hospital LOS and duration of mechanical ventilation.

The association between benzodiazepine-based sedation strategies and delirium has been suggested in prior literature [8 17 18]. The importance of these findings should not be understated as patients with delirium suffer prolonged hospital stays, an increased risk of mortality and long term cognitive impairment[7 8]. Sedation using multiple agents was also associated with increased delirium risk, duration of mechanical ventilation, ICU LOS and

hospital LOS. Whether these effects are a direct result from the sedation strategy, the resulting delirium or as a result of other aspects of their critical illness is unclear.

We also re-confirmed the association between midazolam dominant sedation strategies and longer mechanical ventilation but not mortality as reported by Lonardo *et al.*[11]. The mechanism between the association of benzodiazepines and mortality is unclear, however prolonged mechanical ventilation is a known risk factor for mortality[28]. A meta-analysis by Ho *et al.* comparing propofol to other sedation strategies did not demonstrate an impact on mortality; however, it did not specifically look at midazolam compared to other benzodiazpines[29]. The heterogeneity in mortality outcomes may be attributable to variation in sedation depth, as early deep sedation is an independent predictor of delayed time to extubation and long term mortality[12]. Therefore, not only agent choice but also sedation depth might contribute to the variation in mortality risk observed with benzodiazepines.

Sedation with midazolam and fentanyl is often selected for patients with significant hemodynamic instability to avoid the negative ionotropic and vasodilatory effects of propofol. In our study, those receiving midazolam dominant sedation strategies demonstrated significantly higher SOFA scores, APACHE II scores on admission and were more likely to receive vasoactive medications and continuous renal replacement. All of these may impact mortality when unaccounted for and may explain the heterogeneity observed in the literature[30]. For example, Lonardo *et al.* did not control for the presence of renal replacement which has been associated with a high rate of mortality in critically ill patients[11 31]. Our use of detailed clinical data for risk adjustment may help explain the differences in mortality compared to prior reports.

A fentanyl dominant sedation strategy was significantly associated with an increased risk of delirium, a composite of delirium or death, ICU LOS, hospital LOS and duration of mechanical ventilation. Prior literature shows associations with delayed extubation when given in the first 48 hours, which supports our findings[12]. What is unclear is whether our result is a direct effect of fentanyl, an indirect effect from resulting complications of fentanyl use, for example a pulmonary embolism or pneumonia, or simply an observed association driven by an unidentified confounder. Fentanyl dominant strategies were associated with increased risk of ICU mortality, 30-day mortality, and at hospital discharge but not 1 year. It is difficult to know what to make of these observations. The relationship between fentanyl use and ICU mortality has been incompletely explored in the literature. The mortality risk associated with fentanyl use may be attributable to prolongations in mechanical ventilation[28]. In our data, the effect of mortality appeared strongest in those receiving only fentanyl and was less robust when used in combination. It is

possible those patients who received fentanyl monotherapy were more critically ill. The baseline characteristics of the fentanyl only subgroup revealed these patients that were older, had a higher vasopressor and CRRT use compared to a propofol only but not a midazolam only strategy(Table S3). However, when fentanyl was the dominant strategy for greater than 6 hours compared to the other two strategies, the association between fentanyl and negative patient centred outcomes was more consistent. This may suggest the detrimental association between fentanyl dominant strategies and patient centred outcomes observed is time dependent. Another possibility could be the immunomodulatory effects of narcotics. The mu-opioid receptor is expressed on macrophages and T-lymphocytes, and chronic administration may increase the risk of bacterial infection[32-34]. Therefore, large doses of fentanyl may contribute to further immune dysregulation thereby placing critically ill patients at risk of infection. A final possibility is the use of fentanyl in the provision of palliative symptom control, therefore the mortality association is a marker of this practice. Further study is required to better delineate the true nature of the association between fentanyl and deleterious patient outcomes in the ICU.

Our studies strength is our large cohort size supported by granular patient detail extracted from a prospectively collected, clinical database representing multiple ICUs and the covariates were rigorously controlled using a propensity matched model[22]. The multicenter study design provides a pragmatic view of how sedation strategies are utilized in clinical practice. Limitations of our study include the possibility of confounding bias due to unmeasured impactful covariates or confounding by indication. Patients receiving midazolam dominant strategies were clearly more critically ill compared to those receiving propofol dominant strategies manifest by higher APACHE II scores, greater vasopressor requirements, and higher rates of renal replacement. To compensate, we conducted propensity score-matched analyses adjusted for known covariates. Additionally, fentanyl and midazolam are often used concurrently and teasing apart the isolated effects of each medication may be challenging. Adjustment with our statistical model should minimize this effect, however, it is possible that unrecognized confounders which are not accounted for in the model could introduce unrecognized bias. Randomized controlled trials would better assess this limitation.

Moreover, we focused primarily on the presence or absence of continuous infusions and did not quantify the impact of independent drug boluses. However, this effect would lessen the association with our primary outcome suggesting our observed associations are conservative. Another limitation is the use of drug duration as a surrogate for the impact of the sedation strategy rather than in vivo plasma concentrations. Patient factors may impact

midazolam metabolism due to differences in age, hepatic or renal dysfunction or co-administration of medications with similar metabolic pathways[35-37]. Finally, the definition of dominant sedation strategy based on longest duration of infusion prior to first ICDSC may be considered arbitrary. It is also possible that the current definition classifies some patients as having one dominant sedation strategy when multiple infusions were discontinued in a noticeably short time frame. However, defining sedation in the setting of multiple agents has been incompletely explored in the literature, therefore novel definitions are required. Our data closely reflects multiple findings previously reported with both midazolam and fentanyl sedation. Furthermore, when restricted to patients who received a dominant sedation strategy for greater than 6 hours, the association between fentanyl dominant strategies and negative patient outcomes was more apparent. This reduces the possibility our findings are pure chance. When thresholds for longer durations of sedation dominance were used, the effects became inconsistent, however may be secondary to the effects of statistical analysis on progressively smaller populations.

Conclusion:

This multi-center, propensity score-matched cohort study demonstrates a novel association between fentanyl dominant sedation strategies and negative outcomes in the ICU. Fentanyl dominant sedation strategies were associated with an increased risk of delirium, a composite of delirium or death, duration of ventilation, ICU LOS and hospital LOS. We also confirmed previous reports including an increased risk of delirium and duration of mechanical ventilation with midazolam dominant sedation strategies. This study highlights the need for additional research to further evaluate potentially negative effects of fentanyl and midazolam based sedation strategies.

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Data Sharing Statement: Raw data were generated at the University of Calgary. Derived data supporting the findings of this study are available from the corresponding author CC on request.

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Tables:

Table 1: Baseline Characteristics

	Overall cohort			**Dominant sedation strategy matched cohorts**			
				Propofol vs. Midazolam matched cohort		Propofol vs. Fentanyl matched cohort	
	Propofol (n=1412)	Fentanyl (n=1069)	Midazolam (n=356)	Propofol (n=356)	Midazolam (n=356)	Propofol (n=866)	Fentanyl (n=866)

Characteristic							
Age, median (IQR)	56 (42-67)	59 (44-69)	59 (46-71)	58 (48-69)	59 (46-71)	57 (46-68)	57 (42-69)
Male, n (%)	843 (59.7)	656 (61.4)	223 (62.6)	227 (63.8)	223 (62.6)	533 (61.5)	520 (60.0)
Admission reason, n (%)							
Medical	791 (56.0)	379 (35.5)	259 (72.8)	253 (71.1)	259 (72.8)	426 (49.2)	379 (43.8)
Surgical	265 (18.8)	405 (37.9)	69 (19.4)	74 (20.8)	69 (19.4)	256 (29.6)	248 (28.6)
Neurological	245 (17.4)	73 (6.8)	19 (5.3)	18 (5.1)	19 (5.3)	76 (8.8)	73 (8.4)
Trauma	109 (7.7)	211 (19.7)	9 (2.5)	11 (3.1)	9 (2.5)	108 (12.5)	166 (19.2)
Location admitted from							
Emergency Room	833 (59.0%)	413 (38.6%)	190 (53.4%)	202 (56.7)	190 (53.4)	441 (50.9)	369 (42.6)
Operating Room/Recovery	278 (19.7%)	399 (37.3%)	59 (16.6%)	63 (17.7)	59 (16.6)	232 (26.8)	271 (31.3)
Hospital Ward	254 (18.0%)	209 (19.6%)	91 (25.6%)	85 (23.9)	91 (25.6)	165 (19.1)	180 (20.8)
Another Hospital	26 (1.8%)	24 (2.2%)	7 (2.0%)	4 (1.1)	7 (2.0)	17 (2.0)	23 (2.7)
Other	21 (1.5%)	24 (2.2%)	9 (2.5%)	2 (0.6)	9 (2.5)	11 (1.3)	23 (2.7)
Charlson score, n (%)							
0	582 (41.2%)	422 (39.5%)	121 (34.0%)	127 (35.7)	121 (34.0)	322 (37.2)	336 (38.8)
1	317 (22.5%)	239 (22.4%)	70 (19.7%)	61 (17.1)	70 (19.7)	201 (23.2)	207 (23.9)
2+	513 (36.3%)	408 (38.2%)	165 (46.3%)	168 (47.2)	165 (46.3)	343 (39.6)	323 (37.3)
Charlson score, median (IQR)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-2)
Admission SOFA score, median (IQR)	6 (4-8)	7 (5-10)	8 (6-11)	8 (5-10)	8 (6-11)	7 (4-9)	7 (4-10)
Admission APACHE II score, median (IQR)	18 (13-24)	19 (14-25)	23 (16-28)	21 (16-27)	23 (16-28)	19 (14-24)	19 (13-26)
Vasoactive medications, n (%)	639 (45.3%)	690 (64.5%)	245 (68.8%)	241 (67.7)	245 (68.8)	526 (60.7)	488 (56.4)
Continuous renal replacement therapy, n (%)	59 (4.2%)	78 (7.3%)	33 (9.3%)	28 (7.9)	33 (9.3)	52 (6.0)	73 (8.4)

Table 2: Sensitivity Analyses examining the relationship between delirium and individual sedation agents prior to first ICDSC assessment

	Overall Cohort			Matched cohorts			
Sedation agent prior to first ICDSC assessment	**Number of patients**	**Ever Delirium, n (%)**	**Adjusted OR (95% CI)[1]**	**Number of patients per group**	**Ever Delirium for propofol patients**	**Ever Delirium, n (%)**	**Propensity score-matched OR for Ever**

					from matched cohorts, n (%)		delirium(95% CI)[2]
Propofol	887	509 (57.4)	1.00 (reference group)	N/A[3]	N/A[3]	N/A[3]	1.00 (reference group)
Fentanyl	158	91 (57.6)	1.04 (0.71-1.52)	152	74 (48.7)	87 (57.2)	1.41 (0.90-2.22)
Midazolam	124	77 (62.1)	1.11 (0.73-1.69)	122	69 (56.6)	75 (61.5)	1.23 (0.74-2.05)
Propofol + Fentanyl	854	543 (63.6)	1.32 (1.06-1.65)	565	323 (57.2)	347 (61.4)	1.19 (0.94-1.51)
Propofol + Midazolam	224	163 (72.8)	1.72 (1.23-2.43)	223	143 (64.1)	162 (72.6)	1.49 (1.00-2.23)
Fentanyl + Midazolam	222	160 (72.1)	1.72 (1.22-2.46)	214	119 (55.6)	153 (71.5)	2.00 (1.34-3.00)
All 3	368	269 (73.1)	1.84 (1.38-2.47)	335	199 (59.4)	241 (71.9)	1.75 (1.27-2.42)

Table 3: Delirium subtype by dominant sedation strategy prior to first ICDSC assessment among patients experiencing delirium for the propensity score-matched cohorts

	Dominant sedation strategy			
	Propofol vs. Fentanyl matched cohort patients experiencing delirium		Propofol vs. Midazolam matched cohort patients experiencing delirium	
Delirium Subtype	Propofol (n=529)	Fentanyl (n=569)	Propofol (n=228)	Midazolam (n=257)
Hyperactive only, n (%)	47 (8.9)	40 (7.0)	15 (6.6)	25 (9.7)
Hypoactive only, n (%)	210 (39.7)	228 (40.1)	104 (45.6)	106 (41.2)
Mixed, n (%)	254 (48.0)	289 (50.8)	103 (45.2)	123 (47.9)
Unable to assess or classify, n (%)	18 (3.4)	12 (2.1)	6 (2.6)	3 (1.2)

Table 4: Sensitivity analyses based on those on a single sedation strategy or those whose sedation strategy was dominant for ≥6 hours over the other 2 strategies.

Outcome	**Dominant Sedation Strategy**	**Propensity score-matched odds ratio, mean ratio or rate ratio (95% CI)[1]**
Delirium ever	Propofol	1.00 (reference group)
	Fentanyl(n=476)	1.29 (0.99-1.69)
	Midazolam(n=231)	**1.64 (1.12-2.41)**
Delirium or ICU death	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.38 (1.05-1.81)**
	Midazolam(n=231)	**1.75 (1.18-2.60)**
ICU Mortality	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.82 (1.18-2.84)**
	Midazolam(n=231)	1.31 (0.73-2.39)
Hospital Mortality	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.69 (1.19-2.42)**
	Midazolam(n=231)	1.50 (0.92-2.49)
Died within 30 days of ICU admission	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.84 (1.27-2.68)**
	Midazolam(n=231)	1.14 (0.69-1.89)
Died within 1 year of ICU admission	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.38 (1.02-1.86)**

	Midazolam(n=231)	1.16 (0.77-1.76)
Died within 1.5 years of ICU admission	Propofol	1.00 (reference group)
	Fentanyl(n=476)	1.25 (0.94-1.66)
	Midazolam(n=231)	1.25 (0.84-1.85)
ICU length of stay, mean ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.23 (1.09-1.39)**
	Midazolam(n=231)	1.01 (0.86-1.20)
Hospital length of stay, mean ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.31 (1.13-1.51)**
	Midazolam(n=231)	1.01 (0.83-1.22)
Duration of invasive ventilation, mean ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.35 (1.14-1.59)**
	Midazolam(n=231)	1.17 (0.94-1.46)
Number of delirium days, rate ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl(n=476)	1.19 (0.99-1.43)
	Midazolam(n=231)	1.11 (0.85-1.44)

[1]Data presented as odds ratios unless otherwise indicated.

Figure Legends:

Figure 1: Cohort diagram

Figure 2: Propensity score-matched odds ratios of delirium by dominant sedation strategy prior to first ICDSC assessment

Figure 3: Forest plot of propensity score-matched mean or rate ratios of secondary outcomes and sedation strategy

Figure 1: Cohort diagram

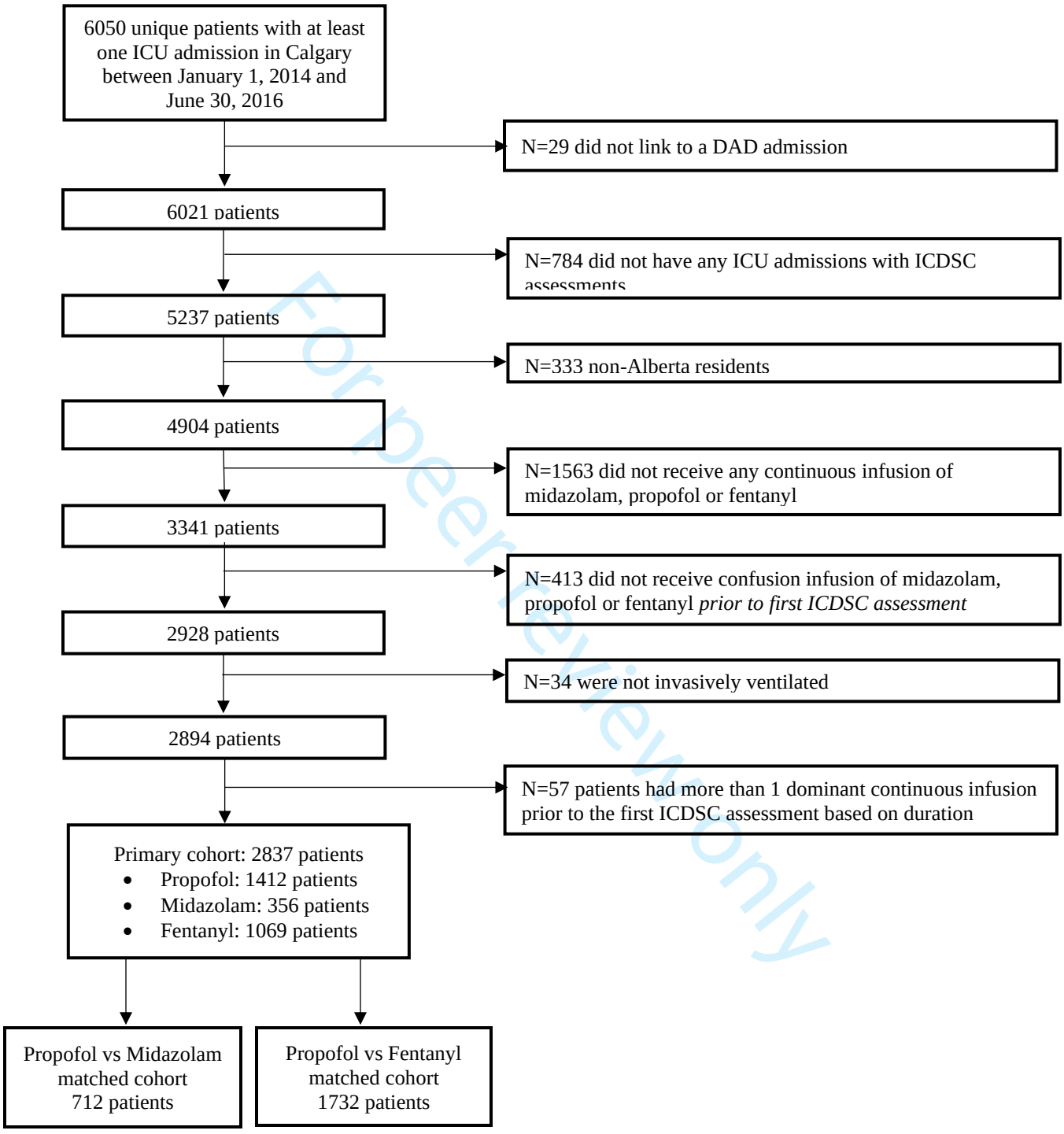

Figure 2: Propensity score-matched odds ratios of delirium by dominant sedation strategy prior to first ICDSC assessment

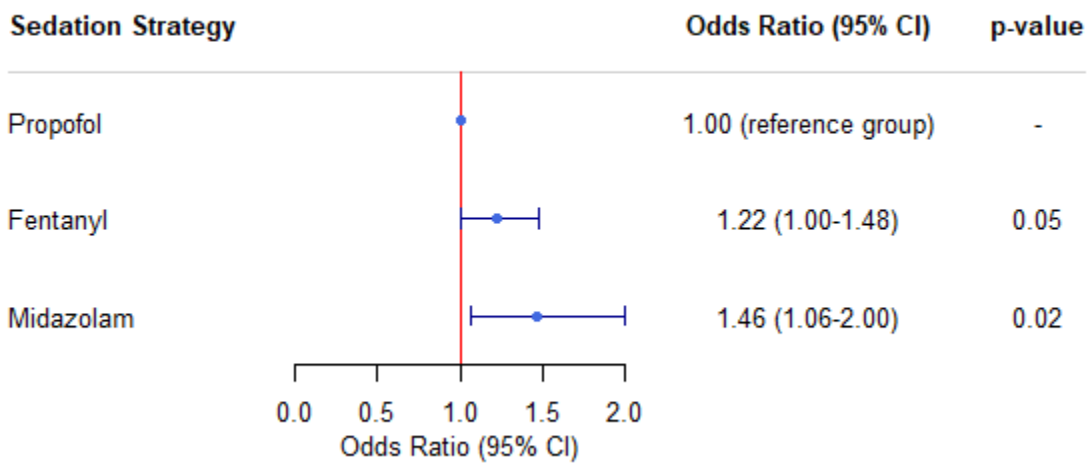

Figure 3: Forest plot of propensity score-matched mean or rate ratios of secondary outcomes and sedation strategy

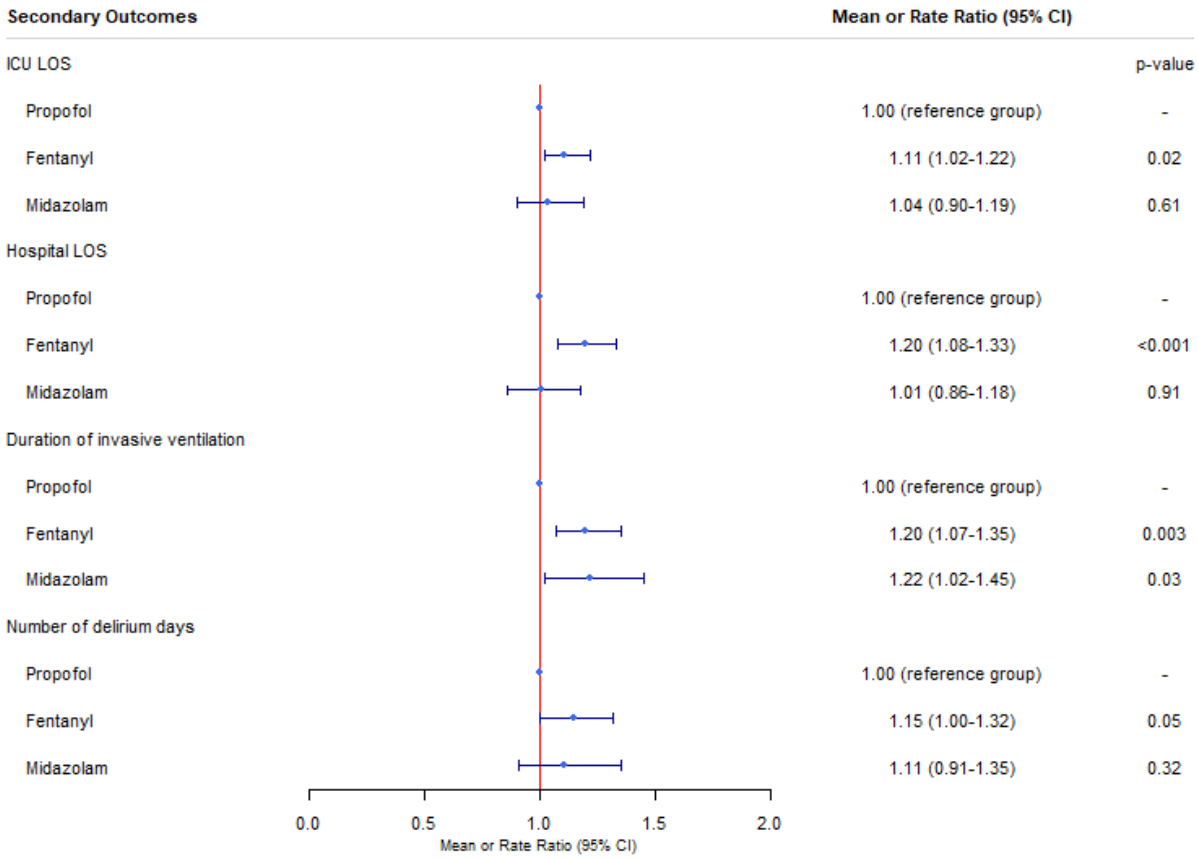

Table S1: Secondary outcomes by sedation strategy prior to first ICDSC assessment

Propensity score-matched mean ratio or rate ratio (95% CI)[1]	**ICU LOS**	**Hospital LOS**	**Duration of invasive ventilation**	**Number of delirium days**
Sedation prior to first ICDSC assessment				
Propofol	1.00 (reference group)	1.00 (reference group)	1.00 (reference group)	1.00 (reference group)
Fentanyl	1.06 (0.85-1.33)	1.25 (0.97-1.61)	1.00 (0.74-1.35)	1.03 (0.69-1.55)
Midazolam	0.83 (0.65-1.06)	0.98 (0.75-1.28)	1.00 (0.73-1.38)	0.88 (0.59-1.31)
Propofol + Fentanyl	**1.17 (1.05-1.30)**	**1.20 (1.05-1.38)**	**1.37 (1.18-1.58)**	1.08 (0.90-1.31)
Propofol + Midazolam	1.16 (0.99-1.36)	0.86 (0.68-1.08)	**1.59 (1.28-1.99)**	1.11 (0.87-1.41)
Fentanyl + Midazolam	**1.40 (1.17-1.67)**	**1.27 (1.02-1.57)**	**1.95 (1.54-2.46)**	1.28 (0.97-1.69)
All 3	**1.73 (1.52-1.98)**	**1.39 (1.18-1.63)**	**2.47 (2.06-2.97)**	**1.35 (1.10-1.67)**

[1]Propensity score based on age, sex, admission class, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, vasoactive medications, continuous renal replacement therapy. 1:1 nearest-neighbor matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score

Table S2: Propensity score matched models of the relationship between mortality outcomes and dominant sedation strategy prior to first ICDSC assessment

Outcome	Dominant Sedation Strategy	Mortality, n (%)	Propensity score-matched OR (95% CI)[2]
ICU Mortality	Propofol	94 (6.7)	1.00 (reference)
	Fentanyl	104 (9.7)	**1.50 (1.07-2.12)**
	Midazolam	39 (11.0)	1.20 (0.74-1.97)
Hospital Mortality	Propofol	157 (11.1)	1.00 (reference)
	Fentanyl	166 (15.5)	1.27 (0.97-1.67)
	Midazolam	59 (16.6)	1.14 (0.76-1.70)
Died within 30 days of ICU admission	Propofol	148 (10.5)	1.00 (reference)
	Fentanyl	148 (13.8)	**1.35 (1.02-1.79)**
	Midazolam	50 (14.0)	1.02 (0.67-1.57)
Died within 1 year of ICU admission	Propofol	268 (19.0)	1.00 (reference)
	Fentanyl	248 (23.2)	1.13 (0.90-1.43)
	Midazolam	91 (25.6)	1.01 (0.72-1.42)
Died within 1.5 years of ICU admission	Propofol	308 (21.8)	1.00 (reference)
	Fentanyl	276 (25.8)	1.12 (0.90-1.40)
	Midazolam	109 (30.6)	1.01 (0.74-1.39)

Supplementary Table 3: Table of baseline characteristics for sensitivity analyses

	Propofol (n=887)	Fentanyl (n=158)	Midazolam (n=124)	Propofol + Fentanyl (n=854)	Propofol + Midazolam (n=224)	Fentanyl + Midazolam (n=222)	All 3 (n=368)
Characteristic							
Age, median (IQR)	58 (46-69)	64 (54-74)	66 (54-74)	55 (40-67)	51 (35-60)	61 (51-71)	52 (40-65)
Male, n (%)	506 (57.0)	79 (50.0)	79 (63.7)	532 (62.3)	145 (64.7)	133 (59.9)	248 (67.4)
Admission reason, n (%)							
Medical	518 (58.5)	59 (37.3)	87 (70.2)	236 (27.7)	176 (78.6)	121 (54.5)	232 (63.0)
Surgical	163 (18.4)	72 (45.6)	30 (24.2)	299 (35.1)	7 (3.1)	81 (36.5)	87 (23.6)
Neurological	169 (19.1)	10 (6.3)	6 (4.8)	102 (12.0)	37 (16.5)	3 (1.4)	10 (2.7)
Trauma	35 (4.0)	17 (10.8)	1 (0.8)	216 (25.3)	4 (1.8)	17 (7.7)	39 (10.6)
Location admitted from							
Emergency Room	520 (58.6)	53 (33.5)	49 (39.5)	367 (43.0)	168 (75.0)	93 (41.9)	186 (50.5)
Operating Room/Recovery	170 (19.2)	62 (39.2)	27 (21.8)	320 (37.5)	6 (2.7)	65 (29.3)	86 (23.4)
Hospital Ward	166 (18.7)	39 (24.7)	43 (34.7)	140 (16.4)	40 (17.9)	49 (22.1)	77 (20.9)
Another Hospital	17 (1.9)	3 (1.9)	2 (1.6)	13 (1.5)	7 (3.1)	7 (3.2)	8 (2.2)
Other	14 (1.6)	1 (0.6)	3 (2.4)	14 (1.6)	3 (1.3)	8 (3.6)	11 (3.0)
Charlson score, n (%)							
0	338 (38.1)	47 (29.7)	30 (24.2)	387 (45.3)	106 (47.3)	74 (33.3)	143 (38.9)
1	204 (23.0)	35 (22.2)	19 (15.3)	171 (20.0)	55 (24.6)	50 (22.5)	92 (25.0)
2+	345 (38.9)	76 (48.1)	75 (60.5)	296 (34.7)	63 (28.1)	98 (44.1)	133 (36.1)

Charlson score, median (IQR)	1 (0-3)	1 (0-3)	2 (1-4)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-2)
Admission SOFA score, median (IQR)	6 (4-8)	8 (5-10)	8 (5-10)	6 (4-9)	7 (5-9)	9 (6-11)	8 (5-11)
Admission APACHE II score, median (IQR)	18 (14-23)	20 (15-26)	23 (16-28)	17 (12-22)	20 914-25)	22 (16-29)	21 (14-26)
Vasoactive medications, n (%)	356 (40.1)	105 (66.5)	81 (65.3)	477 (55.9)	117 (52.2)	175 (78.8)	263 (71.5)
Continuous renal replacement therapy, n (%)	35 (3.9)	10 (6.3)	9 (7.3)	41 (4.8)	7 (3.1)	32 (14.4)	36 (9.8)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, 6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6, Supplement methods
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	4, 7 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	7 Table 2, 3,

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2,3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Sedation strategy and ICU Delirium: A multi-center, population-based propensity score-matched cohort study

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Manuscript: 356 words
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Figures: 3

Conflicts of Interest: No author has a conflict of interest to declare.

Keywords: Delirium, ICU sedation, fentanyl sedation, midazolam sedation

Objectives: We examined the relationship between dominant sedation strategy, risk of delirium, and patient-centered outcomes in adults admitted to intensive care units(ICUs).

Design: Retrospective propensity-matched cohort study.

Setting: Mechanically-ventilated adults (≥ 18 years) admitted to four Canadian hospital medical/surgical ICUs from 2014 – 2016 in Calgary, Alberta, Canada.

Participants: 2837 mechanically-ventilated adults (≥ 18 years) requiring admission to a medical/surgical ICU were evaluated for the relationship between sedation strategy and delirium.

Interventions: None.

Primary and secondary outcome measures: The primary exposure was dominant sedation strategy, defined as the sedative infusion, including midazolam, propofol or fentanyl, with the longest duration before the first delirium assessment. The primary outcome was 'ever delirium' identified using the Intensive Care Delirium Screening Checklist (ICDSC). Secondary outcomes included mortality, length of stay (LOS), ventilation duration, and days with delirium. The cohort was analyzed in two propensity score (patient characteristics and therapies received) matched cohorts (propofol vs. fentanyl and propofol vs. midazolam).

Results: 2,837 patients (60.7% male; median age 57 years (interquartile range 43-68)) were considered for propensity matching. In propensity score-matched cohorts(propofol vs. midazolam, n=712; propofol vs. fentanyl, n=1,732), the odds of delirium were significantly higher with midazolam (odds ratio (OR) 1.46 (95% confidence interval(CI) 1.06-2.00)) and fentanyl (OR 1.22 (95% CI 1.00-1.48)) compared to propofol dominant sedation strategies. Dominant sedation strategy with midazolam and fentanyl were associated with a longer duration of ventilation compared to propofol. Fentanyl was also associated with increased ICU mortality(OR 1.50 (1.07-2.12)) ICU and hospital LOS compared to a propofol dominant sedation strategy.

Conclusions: We identified a novel association between fentanyl dominant sedation strategies and an increased risk of delirium, a composite outcome of delirium or death, duration of mechanical ventilation, ICU LOS, and hospital LOS. Midazolam dominant sedation strategies were associated with increased delirium risk and mechanical ventilation duration.

Article Summary:

- We examine the effects of midazolam and fentanyl sedation strategies on delirium and patient-centered outcomes using a large cohort of general intensive care patients.
- To reduce bias, we used a propensity score matching process on an extensive database.
- One fundamental limitation is secondary to the concurrent use of multiple overlapping sedation strategies, which may impact the results.
- Based on the limitations and the nature of cohort studies, this study as hypothesis-generating.

Introduction:

Delirium in critically ill patients is an acute confusional state marked by severe disorganization of cognition, fluctuating course, attentional deficit, and a disturbance of awareness[1]. Older age, severity of illness, presence of mechanical ventilation, coma, and sedative medications place over 50% of ICU patients at risk for developing delirium[2-6]. Delirium in the ICU is common and may prolong hospital stay, increase mortality risk and contribute to long-term cognitive impairment[7 8]. With a burgeoning elderly population, ICU admission requiring mechanical ventilation is estimated to increase by 80% by 2026; therefore understanding potential contributors to delirium is paramount[9 10].

Over-sedation in the ICU, with benzodiazepines, in particular, may be harmful[11,12]. Prospective cohort and randomized controlled trials support shorter durations of mechanical ventilation, more rapid awakening with propofol or dexmedetomidine than midazolam [13-17]. Similarly, a population-based study by Lonardo *et al.* demonstrated higher mortality, longer duration of mechanical ventilation, and longer ICU length of stay (LOS) in patients managed with benzodiazepines compared to propofol[11]. Lonardo *et al.* postulated midazolam's mortality effect might be due to increased rates of delirium. Delirium is associated with mortality, and some evidence supports patients treated with benzodiazepines may demonstrate higher rates of delirium in the ICU[8 13 18 19]. However, the association between benzodiazepines and delirium is inconsistent[6].

Sedation strategies often employ both a sedative, like propofol, and an analgesic, like fentanyl, simultaneously to achieve the desired effect. However, studies evaluating the clinical effects of these sedation strategies are lacking. Additional research is necessary to understand the effects of sedation strategies on delirium, hospital length of stay (LOS), and survival outcomes. Our study examined the relationship between dominant sedation strategy (continuously infused propofol, fentanyl, and/or midazolam), delirium, and important patient-centered outcomes, in a multi-center population-based sample of mechanically-ventilated adults admitted to ICU.

Methods:

Ethics Approval Statement:

This retrospective cohort study was reported in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[20] and approved by the conjoint health research ethics board at the University of Calgary (REB17-0389).

Patient & Public Involvement Statement:

Neither patients, nor the public were not involved in the design, collection, compilation or completion of this research study.

Study Setting & Population:

We identified consecutive mechanical ventilated adults (≥ 18 years) admitted to four medical-surgical ICUs in Calgary, Alberta, Canada between January 1, 2014, to June 30th, 2016. Patients were excluded if:

1) Their ICU electronic health data did not link to an appropriate inpatient (hospital) admission
2) They did not have any ICU admissions with at least 1 Intensive Care Delirium Screening Checklist (ICDSC) assessment (details described in the *Outcome Measures* section)
3) They were non-Alberta residents (to allow for mortality outcome follow-up post hospital discharge)
4) They did not receive at least 1 continuous infusion of midazolam, propofol or fentanyl prior to the first ICDSC assessment.
5) They were never invasively ventilated during their ICU stay.
6) They did not have a single dominant continuous infusion prior to the first ICDSC assessment (see definition of dominant sedation strategy in the *Exposure Measure* section below for further detail).

If the patient was readmitted to ICU more than once during the study period, then only the first admission with at least 1 ICDSC assessment was used. The ICUs are staffed by accredited intensive care physicians which provide mechanical ventilation, vasoactive medications, and invasive monitoring.

Data sources:

Study data was derived from three electronic databases[21-23]. eCritical Alberta, a database and electronic medical record, that prospectively captures detailed clinical and demographic information[22]. The discharge abstract database (DAD) captures data on all hospitalized patients, including admission date, discharge, survival status, and up to 25 diagnostic codes from the International Classification of Diseases, 10th revision, Canadian enhancement. Out of hospital deaths were obtained from Alberta Vital Statistics, which captures all deaths occurring in Alberta. Data from Alberta Vital Statistics was available up to December 30, 2017, which provided at least 18 months of follow-up from the ICU admission date.

Exposures and Definitions:

The main study exposure was dominant sedation strategy prior to the first ICDSC assessment. A sedation strategy was defined as a continuous analgo-sedative infusion limited to midazolam, fentanyl, and propofol.

Infusions were selected based on a screening survey which demonstrated small populations utilizing alternative sedation strategies. There were seven possible combinations for the sedation strategy prior to the first ICDSC assessment: 1) propofol only, 2) fentanyl only, 3) midazolam only, 4) propofol and fentanyl, 5) propofol and midazolam, 6) fentanyl and midazolam, and 7) all three agents. A high number of patients received more than 1 agent, therefore we classified patients into a dominant sedation strategy, defined as the longest continuous duration of infusion prior to the first ICDSC assessment, which consists of three categories for the primary analyses. For example, if fentanyl was provided for the longest duration, fentanyl was considered the dominant sedation strategy. It is possible the patient could have received propofol or midazolam (or neither) for a duration less than fentanyl. If the patient received two agents for the same duration, the patient was excluded as no strategy was dominant. As sensitivity analyses, all seven possible combinations of the sedation strategy used prior to the first ICDSC assessment were considered.

Outcome Measures:

The primary outcome was categorized as 'ever/never delirium' during ICU admission compatible with previously established delirium outcome measures[7]. All ICU patients with a Richmond Agitation Sedation Scale(RASS)[24] score ≥-3 were evaluated twice daily using the ICDSC tool[25] and received a protocolized sedation awakening trial. The ICDSC is a validated delirium assessment tool[25]. Ever delirium patients were those with an *ICDSC score* ≥4; never delirium were those with an *ICDSC score* <4. Total number of days with an *ICDSC score* ≥4 defined delirium duration. Duration of delirium (days) was examined in secondary analyses.

Delirium motor subtypes were identified using the RASS, based on previously published criteria[18], and associated positive ICDSC score of ≥4. The scale is scored from -5 points (unarousable) to 0 points (calm) to +4 points (combative), where scores between -3 to 0 indicate hypoactive delirium, scores between 1 to 3 indicate hyperactive delirium, and scores that fluctuate between hypoactive and hyperactive indicate mixed delirium. All ICDSC scores ≥4 were linked to the closest RASS score within 4 hours of charting. If there was no RASS score documented within 4 hours of the ICDSC score, the sub-type was considered "unable to be classified". If there was a RASS score within 4 hours of the ICDSC score but the RASS was -5, -4 or +4, the sub-type was considered "unable to be assessed". If at least 1 assessment indicated hypoactive delirium and at least 1 assessment indicated hyperactive delirium the sub-type was considered mixed for that specific patient.

Secondary outcomes were mortality in the ICU and hospital, duration of mechanical ventilation, and ICU & hospital lengths of stay (LOS). Patient mortality was also reported at 30-days and 1-year. Duration of invasive mechanical ventilation was defined as the time a patient required the use of invasive ventilator.

Statistical Analysis:

Baseline characteristics were summarized using median with interquartile range (IQR) and frequency with percent and compared between sedation strategies using chi-squared tests and Kruskal-Wallis rank sum tests, as appropriate. For the primary outcome analysis, logistic regression was used to assess the association between dominant sedation strategy (propofol vs midazolam vs fentanyl) and risk of developing delirium. The relationship between dominant sedation strategy and delirium duration was analyzed using negative binomial models. The relationship between dominant sedation strategy and mortality outcomes were analyzed using logistic regression models. The relationship between dominant sedation strategy and LOS outcomes (ICU and hospital) were analyzed using linear regression models with a log-transformation of ICU LOS and hospital LOS. Primary analyses for all outcomes were based on forming two propensity score-matched cohorts: 1) propofol vs fentanyl and 2) propofol vs midazolam.

The study team considered the following prior to matching including, all measured baseline covariates, all baseline covariates that are associated with treatment assignment (eg. sedation strategy), all baseline covariates that affect the outcome (ie. potential confounders) or all covariates that affect both treatment assignment and outcome (ie. true confounders). Therefore, age, sex, reason for admission, admission APACHE II, the charlson comorbidity index(0,1,2+), use of vasoactives and renal replacement represented covariates which affected the outcome variables and therefore were controlled to ensure patient severity and medical issues did not confound the outcome of the treatment assignment.

The cohorts were formed based on 1:1 nearest-neighbor matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score[26]. Sensitivity analyses were based on the full cohort with models adjusted a priori for the same patient characteristics used in the propensity scores. The above analyses were repeated for the 7-category sedation strategy prior to the first ICDSC assessment. For these analyses, we formed six pairwise propensity score-matched cohorts similar to the primary analyses, matching with patients on propofol only for each of the other 6 categories of sedation strategy prior to the first ICDSC assessment. A two-sided p-value < 0.05 was considered statistically

significant. Analyses were conducted in R, version 3.5.1.[27] Propensity-score matching was performed using the R package "MatchIt", version 3.0.2. Additionally, to control for the competing effects of delirium and death, a sensitivity analysis of a composite endpoint of delirium or death was calculated.

Results:

There were 2,837 patients in the study cohort (Figure 1), which included 1412 patients (49.8%) receiving a propofol dominant strategy, 356 patients (12.5%) receiving a midazolam dominant strategy and 1069 patients (37.7%) receiving a fentanyl dominant strategy. For those receiving propofol dominant sedation, it was common to receive a single agent of only propofol (62.8%). While among those receiving fentanyl and midazolam dominant sedation strategies, single agent use was less common with 14.8% and 34.8% only receiving a single agent, respectively." Most patients were male (60.7%) with a median age of 57 (IQR 43-68) years and admitted for a medical reason (50.4%). The median Charlson comorbidity score was 1 (IQR 0-2), admission SOFA score 7 (IQR 4-9) and admission APACHE II score 19 (IQR 14-25). Patients who received a midazolam dominant sedation strategy were more likely admitted for medical reasons (72.8%) and had higher Charlson comorbidity scores, admission SOFA scores and admission APACHE II scores than those receiving propofol and fentanyl dominant sedation strategies. Patients receiving midazolam dominant strategies were also more likely to receive vasoactive medications (68.8%) compared to those predominantly receiving propofol (45.3%) and fentanyl dominant sedation strategies (64.5%). (Table 1).

Due to missing patient characteristics for 5 patients (0.2%), propensity scores were calculated for 1,409 patients receiving propofol dominant strategies, 1,067 patients receiving fentanyl dominant sedation strategies and 356 patients receiving midazolam dominant sedation strategies. Of the patients receiving fentanyl dominant sedation strategies, 201 (18.8%) could not be matched to a patient receiving propofol dominant sedation strategies within the specified caliper width of 0.2; therefore, this resulted in a matched cohort for propofol and fentanyl of 1,732 patients. Of the patients receiving midazolam dominant sedation strategies, all 356 patients could be matched to a patient receiving propofol dominant sedation strategies; therefore, this resulted in a matched cohort for patients with propofol and midazolam dominant sedation strategies of 712 patients. After matching, the baseline characteristics were balanced(Table 1). The median time from admission to first ICDSC in hours were similar between the propofol(median time = 17.1hrs (IQR = 8.5-34.7)), midazolam((median time =17.6 hrs (IQR = 8.8-41.2)) and fentanyl (median time =16.5 hrs (8.8-35.4) dominant strategies. Additionally, the median number of ICDSC

assessments per ICU day was similar for propofol(1.4 (IQR =1.0-1.8) , fentanyl(1.4 (IQR 1.0-1.8), midazolam(1.3 (IQR 1.0-1.7) dominant sedation strategies.

In the propensity score-matched cohorts, there was a statistically significant association between delirium and midazolam dominant(odds ratio[OR] 1.46 (95% confidence interval 1.06-2.00); p=0.02) as well as fentanyl dominant (OR 1.22 (95% CI 1.00-1.48); p=0.05) sedation strategies compared to propofol dominant sedation strategies(Figure 2). To control for the effects of death on delirium rates, a sensitivity analysis of the matched cohort was performed using a composite outcome of delirium or death. A statistically significant association between the composite outcome of delirium and death with midazolam dominant(OR 1.53 (95% CI 1.10-2.12; p=0.011) and fentanyl dominant(OR 1.27 (95% CI 1.04-1.55; p=0.020) strategies was observed, however not for propofol dominant strategies. Sensitivity analyses based on the 7-category sedation strategy prior to the first ICDSC assessment showed an increased odds of delirium for those on more than one agent compared to those on propofol only (Table 2). Among those who ever experienced delirium, the distribution of delirium subtypes was similar between dominant sedation strategies (Table 3). Based on the propensity score-matched cohorts, a fentanyl dominant sedation strategy was associated with longer duration of mechanical ventilation, longer ICU and hospital LOS and more delirium days compared to a propofol dominant sedation strategy, while a midazolam dominant sedation strategy was associated with a longer duration of mechanical ventilation compared to a propofol dominant sedation strategy(Figure 3). Sensitivity analyses of the secondary outcomes and cohort characteristics based on the 7-category sedation strategy can be found in the supplementary results(Supplementary Digital Content - Table 1 & Table 2, respectively). There was a statistically significant association between fentanyl dominant sedation strategy and ICU(OR=1.50 (1.07-2.12)) and 30-day mortality(OR=1.35 (1.02-1.79)) in propensity score-matched analyses(Supplementary Digital Content - Table 3). An additional sensitivity analysis of the same propensity score-matched cohort evaluating sedation strategy dominance for greater than 6 hours can be found in Table 4. This analysis demonstrated a statistically significant association between fentanyl dominant strategies and a composite of delirium or death, ICU mortality, hospital mortality, 30 day mortality, 1 year mortality, hospital length of stay and duration of mechanical ventilation.

Discussion:

Sedative strategies may increase the risk of adverse patient complications such as delirium, or prolonged mechanical ventilation. We found a midazolam dominant sedation strategy was associated with increased risk of

developing delirium, duration of mechanical ventilation, and a composite of delirium and death. Alternatively, fentanyl was associated with multiple detrimental outcomes including an increased risk of delirium, a composite outcome of delirium or death, ICU & hospital LOS and duration of mechanical ventilation.

The association between benzodiazepine-based sedation strategies and delirium has been suggested in prior literature [8 17 18]. The importance of these findings should not be understated as patients with delirium suffer prolonged hospital stays, an increased risk of mortality and long term cognitive impairment[7 8]. Sedation using multiple agents was also associated with increased delirium risk, duration of mechanical ventilation, ICU LOS and hospital LOS. Whether these effects are a direct result from the sedation strategy, the resulting delirium or as a result of other aspects of their critical illness is unclear.

We also re-confirmed the association between midazolam dominant sedation strategies and longer mechanical ventilation but not mortality as reported by Lonardo *et al.*[11]. The mechanism between the association of benzodiazepines and mortality is unclear, however prolonged mechanical ventilation is a known risk factor for mortality[28]. A meta-analysis by Ho *et al.* comparing propofol to other sedation strategies did not demonstrate an impact on mortality; however, it did not specifically look at midazolam compared to other benzodiazpines[29]. The heterogeneity in mortality outcomes may be attributable to variation in sedation depth, as early deep sedation is an independent predictor of delayed time to extubation and long term mortality[12]. Therefore, not only agent choice but also sedation depth might contribute to the variation in mortality risk observed with benzodiazepines.

Sedation with midazolam and fentanyl is often selected for patients with significant hemodynamic instability to avoid the negative ionotropic and vasodilatory effects of propofol. In our study, those receiving midazolam dominant sedation strategies demonstrated significantly higher SOFA scores, APACHE II scores on admission and were more likely to receive vasoactive medications and continuous renal replacement. All of these may impact mortality when unaccounted for and may explain the heterogeneity observed in the literature[30]. For example, Lonardo *et al.* did not control for the presence of renal replacement which has been associated with a high rate of mortality in critically ill patients[11 31]. Our use of detailed clinical data for risk adjustment may help explain the differences in mortality compared to prior reports.

A fentanyl dominant sedation strategy was significantly associated with an increased risk of delirium, a composite of delirium or death, ICU LOS, hospital LOS and duration of mechanical ventilation. Prior literature shows associations with delayed extubation when given in the first 48 hours, which supports our findings[12]. What is

unclear is whether our result is a direct effect of fentanyl, an indirect effect from resulting complications of fentanyl use, for example a pulmonary embolism or pneumonia, or simply an observed association driven by an unidentified confounder. Fentanyl dominant strategies were associated with increased risk of ICU mortality, 30-day mortality, and at hospital discharge but not 1 year. It is difficult to know what to make of these observations. The relationship between fentanyl use and ICU mortality has been incompletely explored in the literature. The mortality risk associated with fentanyl use may be attributable to prolongations in mechanical ventilation[28]. In our data, the effect of mortality appeared strongest in those receiving only fentanyl and was less robust when used in combination. It is possible those patients who received fentanyl monotherapy were more critically ill. The baseline characteristics of the fentanyl only subgroup revealed these patients that were older, had a higher vasopressor and CRRT use compared to a propofol only but not a midazolam only strategy(Table S3). However, when fentanyl was the dominant strategy for greater than 6 hours compared to the other two strategies, the association between fentanyl and negative patient centred outcomes was more consistent. This may suggest the detrimental association between fentanyl dominant strategies and patient centred outcomes observed is time dependent. Another possibility could be the immunomodulatory effects of narcotics. The mu-opioid receptor is expressed on macrophages and T-lymphocytes, and chronic administration may increase the risk of bacterial infection[32-34]. Therefore, large doses of fentanyl may contribute to further immune dysregulation thereby placing critically ill patients at risk of infection. A final possibility is the use of fentanyl in the provision of palliative symptom control, therefore the mortality association is a marker of this practice. Further study is required to better delineate the true nature of the association between fentanyl and deleterious patient outcomes in the ICU.

Our studies strength is our large cohort size supported by granular patient detail extracted from a prospectively collected, clinical database representing multiple ICUs and the covariates were rigorously controlled using a propensity matched model[22]. The multicenter study design provides a pragmatic view of how sedation strategies are utilized in clinical practice. Limitations of our study include the possibility of confounding bias due to unmeasured impactful covariates or confounding by indication. Patients receiving midazolam dominant strategies were clearly more critically ill compared to those receiving propofol dominant strategies manifest by higher APACHE II scores, greater vasopressor requirements, and higher rates of renal replacement. To compensate, we conducted propensity score-matched analyses adjusted for known covariates. Additionally, fentanyl and midazolam are often used concurrently and teasing apart the isolated effects of each medication may be challenging. Adjustment

with our statistical model should minimize this effect, however, it is possible that unrecognized confounders which are not accounted for in the model could introduce unrecognized bias. Randomized controlled trials would better assess this limitation.

Moreover, we focused primarily on the presence or absence of continuous infusions and did not quantify the impact of independent drug boluses. However, this effect would lessen the association with our primary outcome suggesting our observed associations are conservative. Another limitation is the use of drug duration as a surrogate for the impact of the sedation strategy rather than in vivo plasma concentrations. Patient factors may impact midazolam metabolism due to differences in age, hepatic or renal dysfunction or co-administration of medications with similar metabolic pathways[35-37]. Finally, the definition of dominant sedation strategy based on longest duration of infusion prior to first ICDSC may be considered arbitrary. It is also possible that the current definition classifies some patients as having one dominant sedation strategy when multiple infusions were discontinued in a noticeably short time frame. However, defining sedation in the setting of multiple agents has been incompletely explored in the literature, therefore novel definitions are required. Our data closely reflects multiple findings previously reported with both midazolam and fentanyl sedation. Furthermore, when restricted to patients who received a dominant sedation strategy for greater than 6 hours, the association between fentanyl dominant strategies and negative patient outcomes was more apparent. This reduces the possibility our findings are pure chance. When thresholds for longer durations of sedation dominance were used, the effects became inconsistent, however may be secondary to the effects of statistical analysis on progressively smaller populations.

Conclusion:

This multi-center, propensity score-matched cohort study demonstrates a novel association between fentanyl dominant sedation strategies and negative outcomes in the ICU. Fentanyl dominant sedation strategies were associated with an increased risk of delirium, a composite of delirium or death, duration of ventilation, ICU LOS and hospital LOS. We also confirmed previous reports including an increased risk of delirium and duration of mechanical ventilation with midazolam dominant sedation strategies. This study highlights the need for additional research to further evaluate potentially negative effects of fentanyl and midazolam based sedation strategies.

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Data Sharing Statement: Raw data were generated at the University of Calgary. Derived data supporting the findings of this study are available from the corresponding author CC on request.

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Tables:

Table 1: Baseline Characteristics

	Overall cohort			**Dominant sedation strategy matched cohorts**			
				Propofol vs. Midazolam matched cohort		Propofol vs. Fentanyl matched cohort	
	Propofol (n=1412)	Fentanyl (n=1069)	Midazolam (n=356)	Propofol (n=356)	Midazolam (n=356)	Propofol (n=866)	Fentanyl (n=866)
Characteristic							
Age, median (IQR)	56 (42-67)	59 (44-69)	59 (46-71)	58 (48-69)	59 (46-71)	57 (46-68)	57 (42-69)
Male, n (%)	843 (59.7)	656 (61.4)	223 (62.6)	227 (63.8)	223 (62.6)	533 (61.5)	520 (60.0)
Admission reason, n (%)							
Medical	791 (56.0)	379 (35.5)	259 (72.8)	253 (71.1)	259 (72.8)	426 (49.2)	379 (43.8)
Surgical	265 (18.8)	405 (37.9)	69 (19.4)	74 (20.8)	69 (19.4)	256 (29.6)	248 (28.6)
Neurological	245 (17.4)	73 (6.8)	19 (5.3)	18 (5.1)	19 (5.3)	76 (8.8)	73 (8.4)
Trauma	109 (7.7)	211 (19.7)	9 (2.5)	11 (3.1)	9 (2.5)	108 (12.5)	166 (19.2)
Location admitted from							
Emergency Room	833 (59.0%)	413 (38.6%)	190 (53.4%)	202 (56.7)	190 (53.4)	441 (50.9)	369 (42.6)
Operating Room/Recovery	278 (19.7%)	399 (37.3%)	59 (16.6%)	63 (17.7)	59 (16.6)	232 (26.8)	271 (31.3)
Hospital Ward	254 (18.0%)	209 (19.6%)	91 (25.6%)	85 (23.9)	91 (25.6)	165 (19.1)	180 (20.8)
Another Hospital	26 (1.8%)	24 (2.2%)	7 (2.0%)	4 (1.1)	7 (2.0)	17 (2.0)	23 (2.7)
Other	21 (1.5%)	24 (2.2%)	9 (2.5%)	2 (0.6)	9 (2.5)	11 (1.3)	23 (2.7)
Charlson score, n (%)							
0	582 (41.2%)	422 (39.5%)	121 (34.0%)	127 (35.7)	121 (34.0)	322 (37.2)	336 (38.8)
1	317 (22.5%)	239 (22.4%)	70 (19.7%)	61 (17.1)	70 (19.7)	201 (23.2)	207 (23.9)
2+	513 (36.3%)	408 (38.2%)	165 (46.3%)	168 (47.2)	165 (46.3)	343 (39.6)	323 (37.3)
Charlson score, median (IQR)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-2)
Admission SOFA score, median (IQR)	6 (4-8)	7 (5-10)	8 (6-11)	8 (5-10)	8 (6-11)	7 (4-9)	7 (4-10)
Admission APACHE II score, median (IQR)	18 (13-24)	19 (14-25)	23 (16-28)	21 (16-27)	23 (16-28)	19 (14-24)	19 (13-26)
Vasoactive medications, n (%)	639 (45.3%)	690 (64.5%)	245 (68.8%)	241 (67.7)	245 (68.8)	526 (60.7)	488 (56.4)
Continuous renal replacement therapy, n (%)	59 (4.2%)	78 (7.3%)	33 (9.3%)	28 (7.9)	33 (9.3)	52 (6.0)	73 (8.4)

Table 2: Sensitivity Analyses examining the relationship between delirium and individual sedation agents prior to first ICDSC assessment

	Overall Cohort			Matched cohorts			
Sedation agent prior to first ICDSC assessment	**Number of patients**	**Ever Delirium, n (%)**	**Adjusted OR (95% CI)[1]**	**Number of patients per group**	**Ever Delirium for propofol patients from matched cohorts, n (%)**	**Ever Delirium, n (%)**	**Propensity score-matched OR for Ever delirium(95% CI)[2]**
Propofol	887	509 (57.4)	1.00 (reference group)	N/A[3]	N/A[3]	N/A[3]	1.00 (reference group)
Fentanyl	158	91 (57.6)	1.04 (0.71-1.52)	152	74 (48.7)	87 (57.2)	1.41 (0.90-2.22)
Midazolam	124	77 (62.1)	1.11 (0.73-1.69)	122	69 (56.6)	75 (61.5)	1.23 (0.74-2.05)
Propofol + Fentanyl	854	543 (63.6)	1.32 (1.06-1.65)	565	323 (57.2)	347 (61.4)	1.19 (0.94-1.51)
Propofol + Midazolam	224	163 (72.8)	1.72 (1.23-2.43)	223	143 (64.1)	162 (72.6)	1.49 (1.00-2.23)
Fentanyl + Midazolam	222	160 (72.1)	1.72 (1.22-2.46)	214	119 (55.6)	153 (71.5)	2.00 (1.34-3.00)
All 3	368	269 (73.1)	1.84 (1.38-2.47)	335	199 (59.4)	241 (71.9)	1.75 (1.27-2.42)

Table 3: Delirium subtype by dominant sedation strategy prior to first ICDSC assessment among patients experiencing delirium for the propensity score-matched cohorts

	Dominant sedation strategy			
	Propofol vs. Fentanyl matched cohort patients experiencing delirium		Propofol vs. Midazolam matched cohort patients experiencing delirium	
Delirium Subtype	Propofol (n=529)	Fentanyl (n=569)	Propofol (n=228)	Midazolam (n=257)
Hyperactive only, n (%)	47 (8.9)	40 (7.0)	15 (6.6)	25 (9.7)
Hypoactive only, n (%)	210 (39.7)	228 (40.1)	104 (45.6)	106 (41.2)
Mixed, n (%)	254 (48.0)	289 (50.8)	103 (45.2)	123 (47.9)
Unable to assess or classify, n (%)	18 (3.4)	12 (2.1)	6 (2.6)	3 (1.2)

Table 4: Sensitivity analyses based on those on a single sedation strategy or those whose sedation strategy was dominant for ≥6 hours over the other 2 strategies.

Outcome	**Dominant Sedation Strategy**	**Propensity score-matched odds ratio, mean ratio or rate ratio (95% CI)[1]**
Delirium ever	Propofol	1.00 (reference group)
	Fentanyl(n=476)	1.29 (0.99-1.69)
	Midazolam(n=231)	**1.64 (1.12-2.41)**
Delirium or ICU death	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.38 (1.05-1.81)**
	Midazolam(n=231)	**1.75 (1.18-2.60)**
ICU Mortality	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.82 (1.18-2.84)**

	Midazolam(n=231)	1.31 (0.73-2.39)
Hospital Mortality	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.69 (1.19-2.42)**
	Midazolam(n=231)	1.50 (0.92-2.49)
Died within 30 days of ICU admission	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.84 (1.27-2.68)**
	Midazolam(n=231)	1.14 (0.69-1.89)
Died within 1 year of ICU admission	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.38 (1.02-1.86)**
	Midazolam(n=231)	1.16 (0.77-1.76)
Died within 1.5 years of ICU admission	Propofol	1.00 (reference group)
	Fentanyl(n=476)	1.25 (0.94-1.66)
	Midazolam(n=231)	1.25 (0.84-1.85)
ICU length of stay, mean ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.23 (1.09-1.39)**
	Midazolam(n=231)	1.01 (0.86-1.20)
Hospital length of stay, mean ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.31 (1.13-1.51)**
	Midazolam(n=231)	1.01 (0.83-1.22)
Duration of invasive ventilation, mean ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl(n=476)	**1.35 (1.14-1.59)**
	Midazolam(n=231)	1.17 (0.94-1.46)
Number of delirium days, rate ratio (95% CI)	Propofol	1.00 (reference group)
	Fentanyl(n=476)	1.19 (0.99-1.43)
	Midazolam(n=231)	1.11 (0.85-1.44)

[1]Data presented as odds ratios unless otherwise indicated.

Figure Legends:

Figure 1: Cohort diagram

Figure 2: Propensity score-matched odds ratios of delirium by dominant sedation strategy prior to first ICDSC assessment

Figure 3: Forest plot of propensity score-matched mean or rate ratios of secondary outcomes and sedation strategy

Figure 1: Cohort diagram

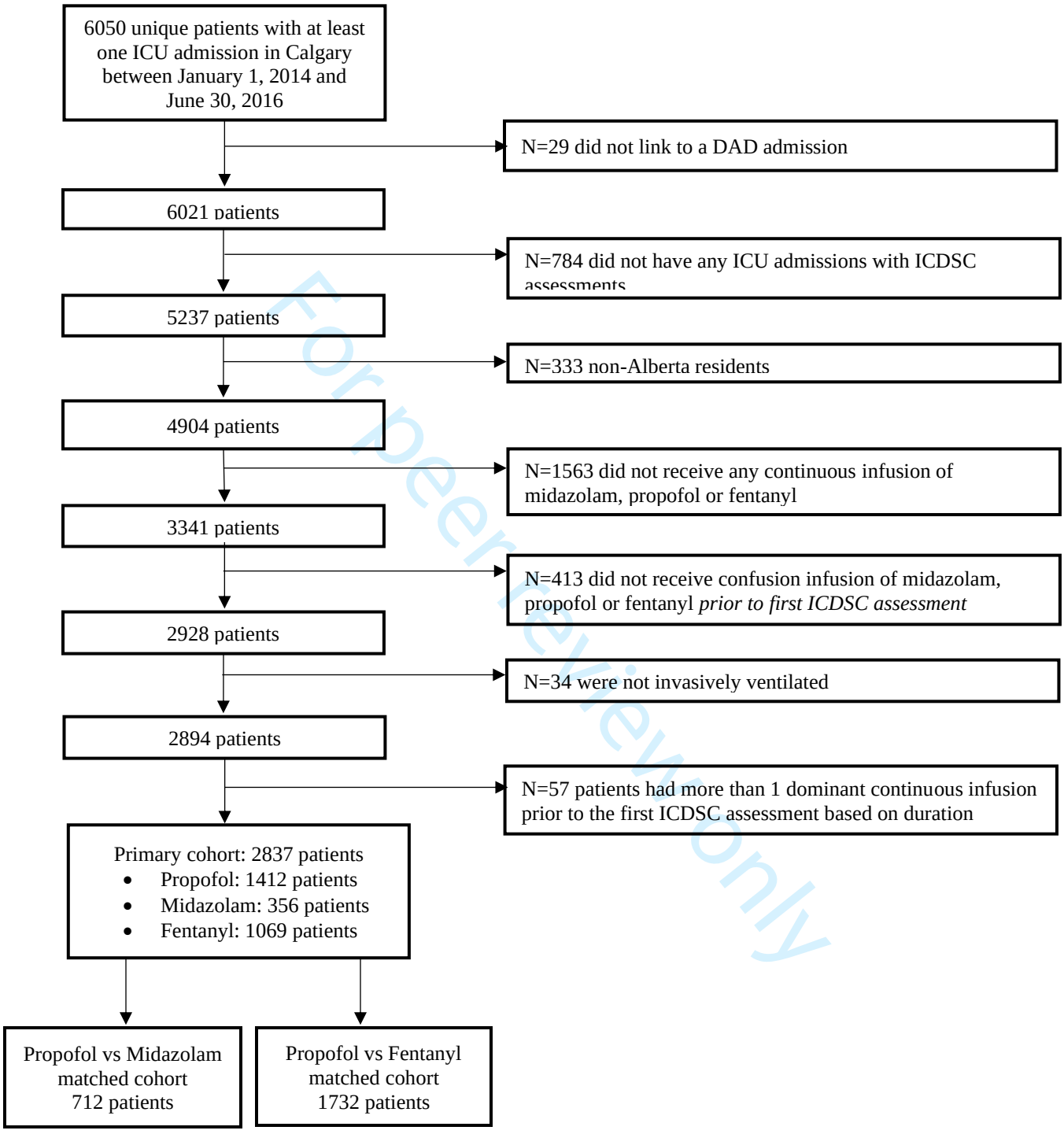

Figure 2: Propensity score-matched odds ratios of delirium by dominant sedation strategy prior to first ICDSC assessment

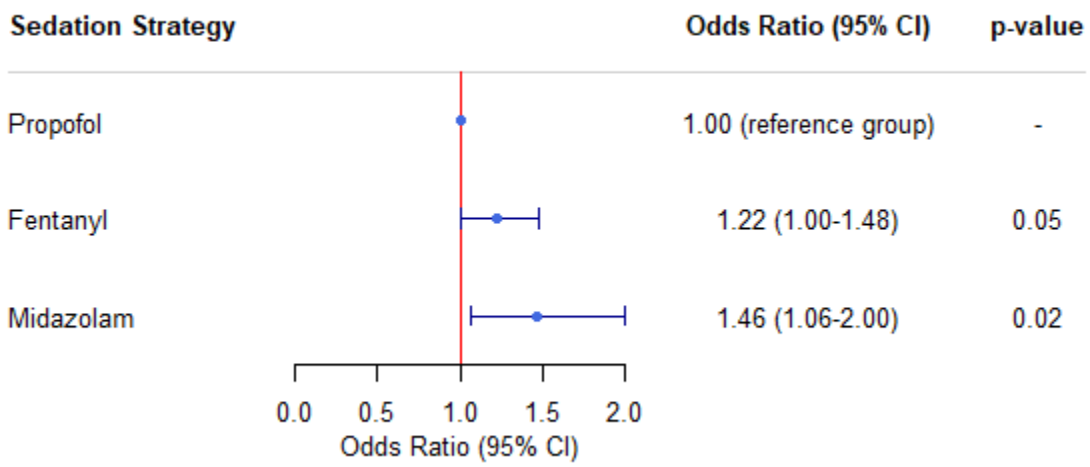

Figure 3: Forest plot of propensity score-matched mean or rate ratios of secondary outcomes and sedation strategy

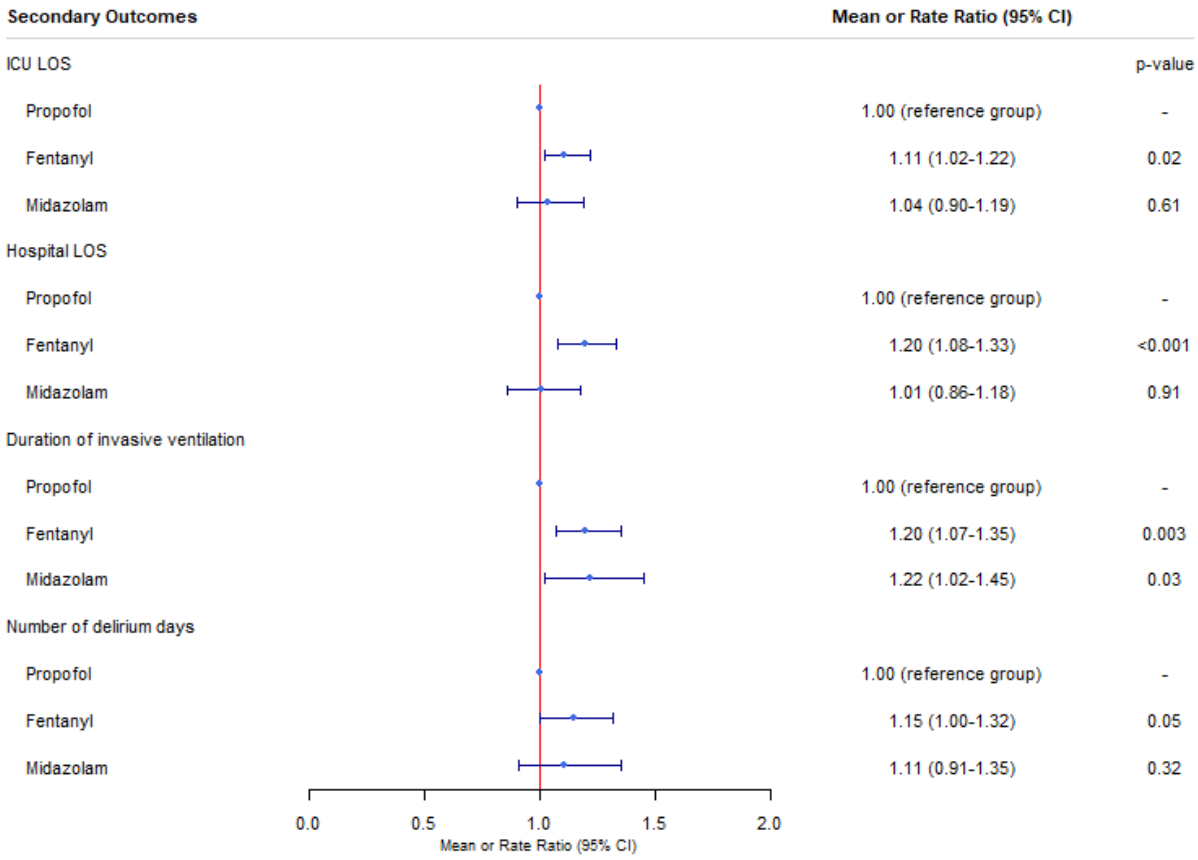

Table S1: Secondary outcomes by sedation strategy prior to first ICDSC assessment

Propensity score-matched mean ratio or rate ratio (95% CI)[1]	**ICU LOS**	**Hospital LOS**	**Duration of invasive ventilation**	**Number of delirium days**
Sedation prior to first ICDSC assessment				
Propofol	1.00 (reference group)	1.00 (reference group)	1.00 (reference group)	1.00 (reference group)
Fentanyl	1.06 (0.85-1.33)	1.25 (0.97-1.61)	1.00 (0.74-1.35)	1.03 (0.69-1.55)
Midazolam	0.83 (0.65-1.06)	0.98 (0.75-1.28)	1.00 (0.73-1.38)	0.88 (0.59-1.31)
Propofol + Fentanyl	**1.17 (1.05-1.30)**	**1.20 (1.05-1.38)**	**1.37 (1.18-1.58)**	1.08 (0.90-1.31)
Propofol + Midazolam	1.16 (0.99-1.36)	0.86 (0.68-1.08)	**1.59 (1.28-1.99)**	1.11 (0.87-1.41)
Fentanyl + Midazolam	**1.40 (1.17-1.67)**	**1.27 (1.02-1.57)**	**1.95 (1.54-2.46)**	1.28 (0.97-1.69)
All 3	**1.73 (1.52-1.98)**	**1.39 (1.18-1.63)**	**2.47 (2.06-2.97)**	**1.35 (1.10-1.67)**

[1]Propensity score based on age, sex, admission class, Charlson comorbidity category (0, 1, 2+), admission APACHE II score, vasoactive medications, continuous renal replacement therapy. 1:1 nearest-neighbor matching without replacement using the logit of the propensity score and specified caliper width equal to 0.2 of the standard deviation of the logit of the propensity score

Table S2: Propensity score matched models of the relationship between mortality outcomes and dominant sedation strategy prior to first ICDSC assessment

Outcome	Dominant Sedation Strategy	Mortality, n (%)	Propensity score-matched OR (95% CI)[2]
ICU Mortality	Propofol	94 (6.7)	1.00 (reference)
	Fentanyl	104 (9.7)	**1.50 (1.07-2.12)**
	Midazolam	39 (11.0)	1.20 (0.74-1.97)
Hospital Mortality	Propofol	157 (11.1)	1.00 (reference)
	Fentanyl	166 (15.5)	1.27 (0.97-1.67)
	Midazolam	59 (16.6)	1.14 (0.76-1.70)
Died within 30 days of ICU admission	Propofol	148 (10.5)	1.00 (reference)
	Fentanyl	148 (13.8)	**1.35 (1.02-1.79)**
	Midazolam	50 (14.0)	1.02 (0.67-1.57)
Died within 1 year of ICU admission	Propofol	268 (19.0)	1.00 (reference)
	Fentanyl	248 (23.2)	1.13 (0.90-1.43)
	Midazolam	91 (25.6)	1.01 (0.72-1.42)
Died within 1.5 years of ICU admission	Propofol	308 (21.8)	1.00 (reference)
	Fentanyl	276 (25.8)	1.12 (0.90-1.40)
	Midazolam	109 (30.6)	1.01 (0.74-1.39)

Supplementary Table 3: Table of baseline characteristics for sensitivity analyses

	Propofol (n=887)	Fentanyl (n=158)	Midazolam (n=124)	Propofol + Fentanyl (n=854)	Propofol + Midazolam (n=224)	Fentanyl + Midazolam (n=222)	All 3 (n=368)
Characteristic							
Age, median (IQR)	58 (46-69)	64 (54-74)	66 (54-74)	55 (40-67)	51 (35-60)	61 (51-71)	52 (40-65)
Male, n (%)	506 (57.0)	79 (50.0)	79 (63.7)	532 (62.3)	145 (64.7)	133 (59.9)	248 (67.4)
Admission reason, n (%)							
Medical	518 (58.5)	59 (37.3)	87 (70.2)	236 (27.7)	176 (78.6)	121 (54.5)	232 (63.0)
Surgical	163 (18.4)	72 (45.6)	30 (24.2)	299 (35.1)	7 (3.1)	81 (36.5)	87 (23.6)
Neurological	169 (19.1)	10 (6.3)	6 (4.8)	102 (12.0)	37 (16.5)	3 (1.4)	10 (2.7)
Trauma	35 (4.0)	17 (10.8)	1 (0.8)	216 (25.3)	4 (1.8)	17 (7.7)	39 (10.6)
Location admitted from							
Emergency Room	520 (58.6)	53 (33.5)	49 (39.5)	367 (43.0)	168 (75.0)	93 (41.9)	186 (50.5)
Operating Room/Recovery	170 (19.2)	62 (39.2)	27 (21.8)	320 (37.5)	6 (2.7)	65 (29.3)	86 (23.4)
Hospital Ward	166 (18.7)	39 (24.7)	43 (34.7)	140 (16.4)	40 (17.9)	49 (22.1)	77 (20.9)
Another Hospital	17 (1.9)	3 (1.9)	2 (1.6)	13 (1.5)	7 (3.1)	7 (3.2)	8 (2.2)
Other	14 (1.6)	1 (0.6)	3 (2.4)	14 (1.6)	3 (1.3)	8 (3.6)	11 (3.0)
Charlson score, n (%)							
0	338 (38.1)	47 (29.7)	30 (24.2)	387 (45.3)	106 (47.3)	74 (33.3)	143 (38.9)
1	204 (23.0)	35 (22.2)	19 (15.3)	171 (20.0)	55 (24.6)	50 (22.5)	92 (25.0)
2+	345 (38.9)	76 (48.1)	75 (60.5)	296 (34.7)	63 (28.1)	98 (44.1)	133 (36.1)

Charlson score, median (IQR)	1 (0-3)	1 (0-3)	2 (1-4)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-2)
Admission SOFA score, median (IQR)	6 (4-8)	8 (5-10)	8 (5-10)	6 (4-9)	7 (5-9)	9 (6-11)	8 (5-11)
Admission APACHE II score, median (IQR)	18 (14-23)	20 (15-26)	23 (16-28)	17 (12-22)	20 914-25)	22 (16-29)	21 (14-26)
Vasoactive medications, n (%)	356 (40.1)	105 (66.5)	81 (65.3)	477 (55.9)	117 (52.2)	175 (78.8)	263 (71.5)
Continuous renal replacement therapy, n (%)	35 (3.9)	10 (6.3)	9 (7.3)	41 (4.8)	7 (3.1)	32 (14.4)	36 (9.8)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, 6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6, Supplement methods
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	4, 7 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	7 Table 2, 3,

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2,3
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.