RESEARCH ARTICLE

Sedative polypharmacy mediates the effect of mechanical ventilation on delirium in critically ill COVID-19 patients: A retrospective cohort study

Somnath Bose[1,2] 🔵 | Lauren Kelly[1,2] 🔵 | Zachary Shahn[3] 🔵 | Lena Novack[2,4] 🔵 | Valerie Banner-Goodspeed[1,2] 🔵 | Balachundhar Subramaniam[1,5] 🔵

[1]Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

[2]Center for Anesthesia Research Excellence (CARE), Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[3]Department of Epidemiology and Biostatistics, CUNY Graduate School of Public Health and Public Policy, New York, New York, USA

[4]Soroka University Medical Center, Beer-Sheva, Israel

[5]Sadhguru Center for a Conscious Planet-Enhancing Consciousness, Cognition, and Compassion, Boston, Massachusetts, USA

Correspondence

Somnath Bose, Department of Anesthesiology Critical Care and Pain Medicine, and Beth Israel Deaconess Medical Center, Harvard Medical School, One Deaconess Rd, Rosenberg 470, Boston, MA 02215, USA.
Email: sbose2@bidmc.harvard.edu

Abstract

Background: Polypharmacy of sedatives (PP) is a potentially modifiable, iatrogenic risk factor for ICU delirium. The extent to which sedative PP influenced development of high rates of delirium among critically ill COVID-19 patients is unknown. We tested the hypothesis that PP, defined as the use of four or more classes of intravenous agents, is a mediator in the causal pathway of mechanical ventilation and delirium.

Methods: Retrospective cohort study of adults admitted with a primary diagnosis of RT-PCR+ for SARS-CoV2 to ICUs of a tertiary-level academic medical center between February 2020 and April 2021. Mediation analysis was conducted with bootstrap estimation to assess whether an association between mechanical ventilation and delirium was mediated by PP. Analyses were adjusted for potential confounders related to mechanical ventilation, mediator, and outcome, including age, gender, vasopressor use, median RASS scores, SOFA score within 24 h of admission, and maximum CRP levels.

Results: A total of 212 patients were included in the analysis. Of total patients, 72.6%(154/212) of patients had delirium (CAM-ICU+) during ICU stay. 54.7%(116/212) patients received PP. Mechanical ventilation (OR 3.81 [1.16–12.52]) and PP (OR 7.38 [2.4–22.68]) were identified as risk factors for development of ICU delirium after adjusting for prespecified confounders. PP acts as a mediator in the causal pathway between mechanical ventilation and delirium. 39% (95% CI: 17%–94%) of the effect of mechanical ventilation on delirium was mediated through PP.

Conclusion: PP mediates approximately 39% of the effect of mechanical ventilation on delirium, which is clinically and statistically significant. Studies should assess whether mitigating PP could lead to reduction in ICU delirium.

Implication Statement: PP of sedatives (defined as use of four or more intravenous agents) mediates approximately 39% of the effect of mechanical ventilation on development of ICU delirium. Avoidance of sedative PP may represent a viable strategy for reduction of ICU delirium.

KEYWORDS

delirium, intensive care unit, mechanical ventilation, mediation analysis, polypharmacy

Editorial Comment

In this retrospective single-center study in critically ill COVID-19 patients, delirium was found in about three out of four patients, while 76.9% were ventilated. Polypharmacy (≥4 classes of sedatives/analgesics) was the strongest risk factor for delirium.

1 | BACKGROUND

Delirium in intensive care units (IiCUs) is associated with significant implications, including cognitive decline, higher risk of institutionalization, and mortality.[1,2] The recent surge in SARS-CoV2 cases exceeding 250 million worldwide (https://coronavirus.jhu.edu/map.html, accessed November 23, 2021), with a sizeable proportion requiring ICU stay, has renewed focus on this problem. Early in the pandemic, estimates of delirium incidence among hospitalized COVID-19 patients varied widely from 20% to 70%, with a recent large international cohort reporting prevalence of 55%.[3–5] Although the pathophysiology of delirium remains complex and poorly understood, several factors, including neurotropism of SARS CoV2, immune-mediated microvascular damage, and microbleeds, have been identified as putative factors.[3,6] Given the unique, infectious nature of the disease, environmental and iatrogenic factors such as the use of deep sedation, prolonged immobilization, fewer sedation holidays, and social isolation are likely contributory as well.[6] Higher nurse-to-patient ratios, capacity surges, anecdotal reports of higher than average sedation requirements, and intermittent drug shortages leading to sedative polypharmacy (PP) have all led to departures from established standards of care.[6,7] The effect of iatrogenic, potentially modifiable factors such as PP on the development of delirium in the study population remains unknown. Since an RCT is neither feasible nor ethical in assessing causal effects of PP, observational studies under certain assumptions could be used to evaluate such effects.[8]

We sought to examine the prevalence of delirium and sedation practices among critically ill COVID-19 patients admitted to ICUs of a tertiary-level academic medical center. To further explore causal associations, we conducted a mediation analysis to estimate the direct effect of mechanical ventilation and indirect effect mediated by PP on the development of delirium among critically ill COVID-19 patients. We tested the hypothesis that sedative PP (defined as the use of four or more classes of intravenous sedative analgesic use) mediates a clinically significant percentage of the effect of mechanical ventilation on the development of delirium in the study population.

2 | SETTINGS AND METHODS

This single-center retrospective cohort study was approved by the Committee on Clinical Investigations and deemed exempt from review (protocol number 2020P000716). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines have been followed in reporting this study.

2.1 | Setting

We analyzed a dataset of critically ill patients who were admitted to the ICUs of a single academic medical center in North America with a primary diagnosis of RT-PCR positive for SARS-CoV2 between February 2020 and April 2021. Our study cohort was restricted to patients who had complete study data as of April 2021.

De-identified data were extracted from the electronic health record and entered directly into a secure institutional REDCap database. We recorded baseline patient characteristics including but not limited to age on ICU admission, race, gender, insurance status, smoking, alcohol use, and comorbidities. We also collected data on hospital and ICU stay, including but not limited to the length of stay, duration of mechanical ventilation, vasopressor support, mortality, delirium assessments (Continuous Assessment Method for ICU [CAM-ICU]), level of sedation (Richmond Agitation and Sedation Scale [RASS]), electrolyte glucose levels, inflammatory marker (C-Reactive Protein), and Day 1 SOFA scores during the ICU stay. Participants were followed up until hospital discharge.

2.2 | Participants

Adult patients (≥18 years) were eligible if they were admitted to the ICUs of the study site between February 2020 and April 2021 with a primary diagnosis of RT-PCR positive for SARS-CoV2. Patients with an ICU stay of fewer than 24 h or with no recorded delirium assessments (i.e., no CAM ICU positive or negative reported values) were excluded. Patients readmitted to ICU during index hospitalization were also excluded from the analysis.

2.3 | Variables

The level of consciousness of all patients admitted to the ICU was assessed by a trained nurse every 4 h using the RASS. RASS is a validated scale used to determine the depth of sedation, and it ranges from −5 to +4. Patients with RASS > −4, that is, −3 to +4, are assessed twice daily for delirium using the CAM-ICU by a trained bedside nurse. CAM-ICU has been shown to have excellent sensitivity, specificity, and inter-rater reliability as a diagnostic test for delirium.[9] Delirium assessments were coded as either present or absent (based on CAM-ICU screening) or unable to assess (comatose) if patients had an RASS score ≤ −4. Delirium, our primary outcome of interest, was coded as positive or negative based on whether the patient had a CAM-ICU positive assessment at *any* point during ICU stay.

Intravenous sedative and analgesic use during ICU stay were classified according to pharmacological categories, namely opioids (OP), benzodiazepines (BZD), propofol (PF), dexmedetomidine (DEX), and ketamine (KM). Categories with multiple members were collapsed into their parent pharmacological class. For example, fentanyl, morphine, hydromorphone, and methadone were collapsed into OP, and lorazepam, diazepam, and midazolam were collapsed into BZD. Sedative PP, our mediator variable of interest, was categorized as yes/no based on whether patients received ≥4 classes of sedatives during their ICU stay. A cut-off of ≥4 classes was used to define PP as the use of up to three classes of medications is common among ICU patients.

3 | STATISTICAL ANALYSES

Descriptive statistics were summarized as means (SD) or median (IQR) for continuous data as appropriate. Categorical variables were reported as frequencies and proportions. We ascertained the association between mechanical ventilation (main exposure of the study) and delirium (outcome), as well as PP (the presumed mediator) in a multivariable analysis. A parsimonious multivariable logistic regression model was created using the following prespecified covariates: age (dichotomized as ≥65 and <65), gender (female vs. male), mechanical ventilation (yes/no), use of vasopressor or inotrope (yes/no), maximum CRP (continuous), median RASS score (continuous), PP (yes/no), and SOFA scores from the first 24 h of ICU admission (continuous) for prediction of delirium (outcome). Model fit characteristics were compared separately with two other prespecified models, one which excluded PP and a second which included substance use and prior history of neurologic or psychiatric disorder as covariates. Akaike's information criteria (AIC) and Bayesian information criteria (BIC) were used to assess the goodness of model fit with lower values indicating better fit. Similar regression was built for predicting PP.

We conducted a mediation analysis to estimate the effect of mechanical ventilation on outcome delirium and the degree to which it is mediated by PP. The average causal mediation effect (ACME) quantifies the impact of a treatment (ventilation) on an outcome (delirium) specifically through a mediator (PP).[10] In our application, it is the contrast between delirium rates that would be observed under two counterfactual scenarios: (A) everybody receives their natural/observed treatment (ventilation) assignments but has their mediator (PP) set to the value it would take had they been treated (ventilated); (B) everybody receives their natural/observed treatment (ventilation) assignments but has their mediator (PP) set to the value it would take had they **not** been treated (ventilated). The average direct effect (ADE) quantifies the impact of a treatment on an outcome *not* through a mediator.[10] In our application, it is the contrast between delirium rates under the following two scenarios: (A) everybody (contrary to fact) is ventilated but receives the PP assignment they would have received under their natural ventilation assignment; and (B) nobody (contrary to fact) is ventilated, but everybody receives the PP assignment they would have received under their natural ventilation assignment. The total effect of ventilation on delirium ignoring mediation is

the sum of the direct (ADE) and indirect (ACME) effects. We used the R (version 4.1.0) mediation package (Tingley et al: https://cran.r-project.org/web/packages/mediation/vignettes/mediation.pdf) to estimate all mediation effects.[11] The mediation analysis required specification of regression models for the outcome and the mediator. We specified a logistic regression model for the outcome given the mediator, treatment, and covariates specified in the parsimonious model above. We also specified a logistic regression model for the mediator given treatment and covariates. Confidence intervals were computed via nonparametric bootstrap with 1000 iterations. All results were considered statistically significant at $p < .05$. R code for mediation analysis is provided in Appendix A in Data S1. STATA 17.0 (Stata Corp.) and SAS 9.4 (SAS Institute) were used for all other analyses.

4 | RESULTS

4.1 | Patient characteristics

Two hundred twelve patients were included in the final analysis (Figure 1). Of total patients, 72.6% (154/212) were assessed to have delirium at least once during their ICU stay; 76.9% (163/212) of the cohort was mechanically ventilated, with 55.2% requiring vasopressor or inotropic support during their stay; 81.1% of patients received OP, followed by 75.9% receiving PF and 60.4% BZD. KM and DEX were used in 40.6% and 54.3% of patients, respectively. PP, defined as the use of four or more classes of sedatives, was used in 54.7% (116/212) patients. 30.2% (64/212) patients died during hospitalization. Further details of hospital stay characteristics are summarized in Table 1. Baseline and clinical characteristics stratified by delirium (D) and non-delirium (ND) status during ICU stay are given in Table 1. Patients with delirium were more likely to have required mechanical ventilation (92.9 vs. 34.5%), vasopressor or inotrope support (66.2 vs. 25.9%), and PP (70.8 vs. 12.1%). The use of sedatives across all classes was significantly higher in the delirium group when compared to the non-
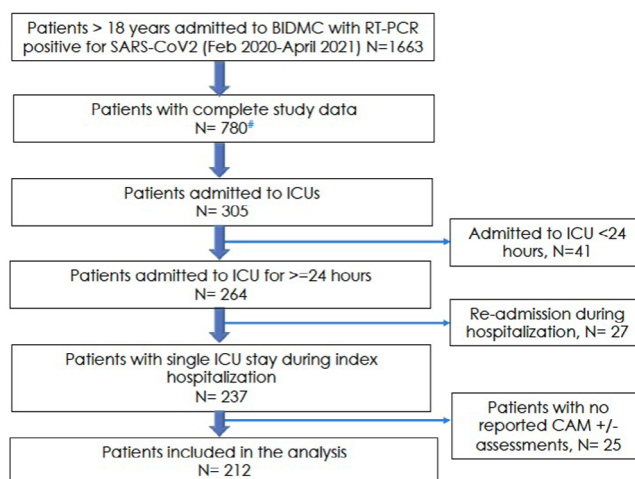

FIGURE 1 Derivation of cohort (#data collection complete as of April 2021)

TABLE 1 Demographics and clinical characteristics of the cohort

Demographics and clinical characteristics	Mean (SD), median (IQR), or proportions (%)			
	Entire cohort (N = 212)	Delirium (n = 154)	No delirium (n = 58)	p-value
Age (years)	64.1 (15.5)	63.4 (15.4)	65.9 (15.7)	.293
Gender, male n (%)	129 (60.9)	89 (57.8)	40 (69.0)	.137
Race, n (%)				.66
White	81 (38.2)	56 (36.4)	25 (43.1)	
African American	53 (25)	40 (26.0)	13 (22.4)	
Other	78 (36.8)	58 (37.7)	20 (24.5)	
Smoking status, n (%)				.982
Nonsmoker	149 (70.3)	108 (70.1)	41 (70.7)	
Current smoker	12 (5.7)	9 (5.8)	3 (5.2)	
Former smoker	51 (24.1)	37 (24.0)	14 (24.1)	
Alcohol or substance abuse, n (%)	18 (8.5)	11 (7.1)	7 (12.1)	.273
Hypertension, n (%)	121 (57.1)	89 (57.8)	32 (55.2)	.731
Coronary disease, n (%)	23 (10.9)	13 (8.4)	10 (17.2)	.066
Obesity, n (%)	46 (21.7)	38 (24.7)	8 (13.8)	.087
Cardiac disease, n (%)	22 (10.4)	13 (8.4)	9 (15.5)	.132
Pulmonary disease, n (%)	40 (18.9)	27 (17.5)	13 (22.4)	.418
Renal disease, n (%)	31 (14.6)	22 (14.3)	9 (15.5)	.821
Liver disease, n (%)	12 (5.7)	10 (6.5)	2 (3.5)	.519
Endocrine disease, n (%)	88 (41.5)	60 (39.0)	28 (48.3)	.22
Malignancy or Immunosuppression, n (%)	17 (8.0)	12 (7.8)	5 (8.6)	.784
Neurologic disease, n (%)	21 (9.9)	15 (9.7)	6 (10.3)	.896
Psychiatric disease, n (%)	31 (14.6)	25 (16.2)	6 (10.3)	.279
Oxygenation method (ever used), n (%)				
Invasive mechanical, ventilation	163 (76.9)	143 (92.9)	20 (34.5)	<.001
Noninvasive ventilation	35 (16.5)	23 (14.9)	12 (20.7)	.314
High flow nasal cannula	32 (15.1)	17 (11.0)	15 (25.9)	.007
Face mask	45 (21.2)	30 (19.5)	15 (25.9)	.311
Nasal cannula	91 (42.9)	59 (38.3)	32 (55.2)	.027
Proning	30 (14.2)	27 (17.5)	3 (5.2)	.021
Vasopressor or inotrope use, n (%)	117 (55.2)	102 (66.2)	15 (25.9)	<.001
Neuromuscular blockade use, n (%)	30 (14.2)	30 (29.5)	0 (0.0)	<.001
Sedatives used by class, n (%)				
Opioids, n (%)	172 (81.1)	146 (94.8)	26 (44.8)	<.001
Benzodiazepines	128 (60.4)	113 (73.4)	15 (25.9)	<.001
Ketamine	86 (40.6)	78 (50.7)	8 (13.8)	<.001
Propofol	161 (75.9)	144 (93.5)	17 (29.3)	<.001
Dexmedetomidine	115 (54.3)	108 (70.1)	7 (12.1)	<.001
Number of sedative classes used, n (%)				<.001
0	37 (17.5)	6 (3.9)	31 (53.5)	
1	7 (3.3)	1 (0.7)	6 (10.3)	
2	22 (10.4)	15 (9.7)	7 (12.1)	
3	30 (14.2)	23 (14.9)	7 (12.1)	
4	59 (27.8)	56 (36.4)	3 (5.2)	
5	57 (26.9)	53 (34.4)	4 (6.9)	
Polypharmacy (use of four or five classes of sedatives)	116 (54.7)	109 (70.8)	7 (12.1)	<.001

TABLE 1 (Continued)

| Demographics and clinical characteristics | Mean (SD), median (IQR), or proportions (%) | | | |
	Entire cohort (N = 212)	Delirium (n = 154)	No delirium (n = 58)	p-value
Maximum CRP	225 (159.2, 276.4)	234.8 (183.1, 277.9)	166.8 (118.2, 273.9)	.004
Median RASS	-2 (−3, −1)	-3 (−4, −1.5)	0 (−1, 0)	<.001
ICU length of stay (days)	11 (7, 20)	16 (8, 23)	5 (3, 9)	<.001
Hospital length of stay (days)	18 (11.5, 28.5)	23 (15, 34)	12.5 (8, 17)	<.001
Mechanical ventilation duration (days)	12.2 (6.8, 20.6)	13 (7.1, 22.1)	7.7 (2.4, 10.3)	<.001
Discharged alive, n (%)	148 (69.8)	104 (67.5)	44 (75.9)	.239
CAM ICU positive, n (%)	154 (72.6)			
SOFA for first 24 h of ICU admission	10 (6, 12)	11 (8, 13)	4 (3, 7)	<.0001

Note: Cardiac disease—arrhythmias, atrial arrhythmias, congestive heart failure, valvular heart disease; renal disease—chronic kidney disease, chronic dialysis, moderate to severe renal disease; liver disease—hepatitis B, hepatitis C, mild–moderate or severe liver disease; endocrine disease—diabetes mellitus (DM), hypothyroidism, DM without end organ, DM with end-organ damage; malignancy or immunosuppression—solid tumor without metastasis, hematologic malignancy, metastatic cancer, solid tumor without metastasis, solid organ or bone marrow transplant, HIV/AIDS or other immunosuppression, leukemia or lymphoma; neurologic disease—stroke or other disorder, paralysis, dementia, cerebrovascular disease mild or no residual or transient ischemic attack, hemiplegia; psychiatric disease—anxiety, depression.
Abbreviations: CAM-ICU, Continuous Assessment Method for ICU; CRP, C-reactive protein; RASS, Richmond Agitation and Sedation Scale.

TABLE 2 Odds of developing delirium based on a multivariable logistic regression model with prespecified covariates

| | Unadjusted | | | Adjusted[a] | | |
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age (≥65 versus <65) (Ref = ≥65 years)	0.89	0.49–1.64	.716	1.72	0.68–4.32	.251
Gender (Ref = Male)	1.62	0.85–3.08	.139	2.50	0.97–6.49	.059
Mechanical ventilation (Ref = Yes)	24.7	10.90–55.97	<.001*	3.81	1.16–12.52	.028*
Vasopressor use (Ref = Yes)	5.62	2.86–11.05	<.001*	1.80	0.67–4.85	.247
Max CRP	1.01	1.00–1.01	<.001*	1.00	1.00–1.01	.265
Median RASS	0.44	0.34–0.57	<.001*	0.88	0.63–1.22	.44
Polypharmacy (Ref = Yes)	17.65	7.45–41.83	<.001*	7.38	2.4–22.68	<.001*
SOFA on first 24 h of ICU admission	1.39	1.26–1.53	<.001*	1.11	0.98–1.26	.105

Note: *p value <.05 considered significant. Age—categorized as ≥65 years and <65 years; polypharmacy (use of four or five classes of intravenous sedatives).
Abbreviations: CRP, C-reactive protein; RASS, Richmond Agitation and Sedation Scale.
[a]Adjusted for age, gender, mechanical ventilation, vasopressor use, CRP (maximum during ICU stay), median RASS, polypharmacy, and SOFA on first 24 h of ICU admission.

delirium group. Median (IQR) RASS scores were significantly lower in the delirium group [−3 (−4, −1.50)] compared to no-delirium group [0 (−1, 0)]. Maximum CRP levels, and SOFA scores from the first 24 h of ICU admission were significantly higher in the delirium group compared to no-delirium group [234 (183.1277.9) vs. 166.8 (118.2273.9)] and [11 (3, 8) vs. 4 (3, 7)] respectively.

4.2 | Risk factors

Upon adjustment for prespecified confounders, use of mechanical ventilation (OR 3.81 [1.16–12.52]) and PP (OR 7.38 [2.4–22.68]) were associated with the development of delirium (Table 2). The
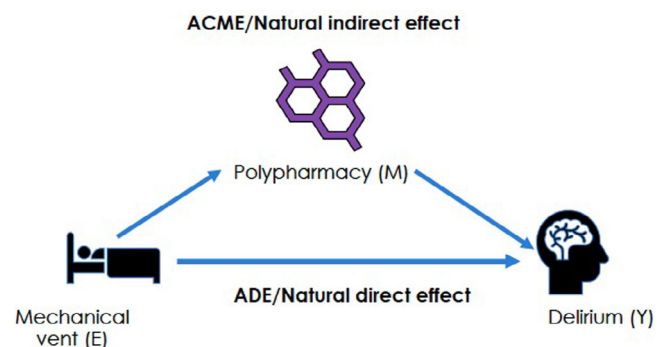

FIGURE 2 DAG demonstrating the relationship between mechanical ventilation, polypharmacy, and delirium

TABLE 3 Nonparametric Bootstrap confidence intervals with the percentile method

	Estimate	Bootstrap 95% CI (N = 1000 simulation)	p-value
Total effect	0.36	0.12–0.67	<.001*
ADE (Average)	0.22	0.01–0.49	.038*
ACME (Average)	0.14	0.05–0.27	<.001*
Proportion mediated through PP (Average)	0.39	0.17–0.94	<.001*

Note: *p value <.05 considered significant. Total effect—effect of mechanical ventilation on delirium ignoring mediation; ADE (average direct effect)—effect of mechanical ventilation on delirium *not* through a mediator (polypharmacy); ACME (average causal mediated effect or indirect effect)—effect of mechanical ventilation on delirium *through* a mediator (polypharmacy); proportion mediated—proportion of total effect of mechanical ventilation on delirium through mediator (polypharmacy).
Abbreviation: CI, confidence interval; PP, polypharmacy.

relationship between delirium and PP persisted when the class of medication used was treated as a continuous exposure (0–5) with OR 1.91 [1.26–2.90] (p = .002). Model fit characteristics and comparison with other candidate nested models are shown in Appendix B in Data S1.

4.3 | Mediation analysis and effect estimation

We adopted a mediation framework (illustrated by the DAG in Figure 2) in which mechanical ventilation can cause delirium either through PP including potentially deliriogenic medications or through other pathways such as immobilization. Results of the mediation analysis are expressed as additive effects on the probability of delirium with 95% CI. The total effect (TE) of mechanical ventilation on delirium through all pathways was estimated to be 0.36 (0.11–0.67). The ADE, which quantifies the effect of exposure (mechanical ventilation) on the outcome *not* through the mediator (PP), was estimated at 0.22 (0.01–0.49). The average causal mediated effect (ACME) or indirect effect, which quantifies the effect of mechanical ventilation on delirium *mediated* by PP, was 0.14 (0.05–0.27). The proportion mediated, that is, the ratio of the indirect effect to the total effect, was estimated at 0.39 (0.17–0.94). Detailed results are shown in Table 3. All results were statistically significant at p < .05. These results suggest that approximately 39% of the effect of mechanical ventilation on delirium was mediated through PP.

5 | DISCUSSION

We investigated the prevalence of delirium and sedation practices in a cohort of critically ill COVID-19 patients admitted to a single North American tertiary-level academic medical center. Further, we sought to investigate the causal effect of PP as a mediator in the pathway between mechanical ventilation and delirium. Sedative PP was common and was used in more than half (54.7%) of patients. Mechanical ventilation and PP were identified as risk factors for delirium after adjusting for prespecified confounders. Using a mediation analysis framework, we found that approximately 39% of the effect of mechanical ventilation on the development of delirium was mediated through PP which is both clinically and statistically significant.

The prevalence of delirium noted in our cohort is consistent with that reported in the literature for COVID-19 patients.[5,6] The use of various classes of sedatives seen in our study, for example, BZD and OP use (60.4% and 81.1%, respectively), was significantly higher than other contemporary non-COVID cohorts.[12] PP, defined as the use of four or more classes of intravenous medications, was also approximately 2.5 times that seen in Pisani et al.'s[12] 2009 study from the pre-COVID era. Robust evidence demonstrating the adverse effects of the more profound depth of sedation and higher use of sedatives have led to the development of guidelines favoring minimization of the depth of sedation and sedatives.[13-16] Current guidelines mirror these and emphasize early mobilization and family presence to reduce delirium burden.[17] Our results stand in stark contrast to the general trends across ICUs worldwide, which noted a decline in delirium rates and sedative use prior to the COVID-19 pandemic.[18,19] The reasons for the trend noted in our cohort are likely multifactorial, as highlighted by Wilcox et al[6]; however, the specific role of PP, a potentially modifiable factor (primarily driven by drug shortages and mostly anecdotal reports of high requirements), had not been systematically examined.[20,21] We specifically examined the role PP of intravenous medications plays in mediating the effects of mechanical ventilation, a well-known risk factor in the development of delirium. The use of up to three sedatives is standard across most ICUs is common and was therefore chosen as the referent category. The relationship between sedative class and delirium remained consistent when treated as a continuous variable (OR 1.91 [1.26–2.90]). The results of our mediation analysis repeated with 1000 bootstrap samplings suggest that approximately 39% of the effect of mechanical ventilation on delirium was mediated *through* the PP pathway. The magnitude of this effect is both statistically and clinically significant and therefore avoidance of polypharmacy may represent a pragmatic strategy which may be helpful in reducing the incidence of delirium. Our small sample size does not allow us to comment on the risk of delirium conferred by specific classes of medications (Appendix C in Data S1) due to wide confidence intervals. Our exploratory results suggest that PP *may* be a more potent driver of delirium than individual medication classes per se. PP, leading to drug interactions, has been associated with poor functional status, diminished executive function, increased delirium, and impaired cognitive function.[22-24] Clearance of sedative agents is frequently impaired due to altered pharmacokinetics in critically ill

patients.[23] We hypothesize that the effects on delirium noted in our cohort could be explained in part by the enhanced pharmacological effects from drug accumulation, and interactions among these classes, each with significant deliriogenic potential. Although mechanical ventilation by other causal pathways (such as immobilization) also contributes to delirium, the decision to initiate mechanical ventilation is often unavoidable and thus practically non-modifiable hence further highlighting the importance of the mediator (PP) in the causal pathway of ICU delirium.

Ours is the first study to decompose the causal pathway between mechanical ventilation and delirium using mediation analysis to identify relative contributions of these factors. We used a cohort of critically ill patients admitted with a primary diagnosis of COVID-19 to a tertiary-level academic medical center in the US during a surge in COVID-19 cases, and therefore, our practices and results are likely reflective of institutions that faced similar logistic constraints. Our study has several limitations. First, the relatively modest sample size and lack of granularity around drug dosage, duration, and temporality do not allow us to examine the relative contribution of various medication classes, which should be the focus of further research. Second, we did not have specific information regarding compliance with components of the ABCDEF bundle, although standard at our institution.[25] Third, we did not have information on the family presence component of the ABCDEF bundle. Visitation restrictions were broadly in effect during the study period therefore lack of this data is unlikely to have biased our results significantly. We acknowledge that lack of data on the compliance with daily awakening, spontaneous breathing trials, and early mobility components of the ABCDEF bundle may have led to an overestimation of the effect size. Nonetheless, the large estimates suggest a *clinically meaningful* proportion of the effect mediated through PP, which is likely modifiable. Finally, the estimation of the total effect of ventilation on delirium (ignoring mediation) depends on the strong assumption that observed covariates were sufficient to adjust for confounding between ventilation and delirium.[26] Mediation results depend on the even stronger assumptions that (a) observed covariates suffice to adjust for confounding of the treatment (ventilation) and the outcome (delirium) as well as confounding of the treatment (ventilation) and the mediator (PP); and (b) observed covariates and treatment (ventilation) together suffice to adjust for confounding of the mediator (PP) and the outcome (delirium).[10] We used a parsimonious multivariable regression model to adjust for confounding using prespecified covariates, which performed better than two other candidate models; however, the presence of residual confounding cannot entirely be ruled out as in most observational studies. Therefore, our results, although strong, should be considered exploratory.

6 | CONCLUSION

In conclusion, we found a very high prevalence of delirium among critically ill COVID-19 patients who were admitted for more than 24 h to a tertiary-level academic medical center in the US. Of total patients, 54.7% of patients received PP, which mediated 39% of the effect of

mechanical ventilation on delirium. Though exploratory, given the high prevalence of delirium and its numerous adverse consequences, avoidance of PP may represent a viable step in the prevention of this condition. The extent to which the risk of delirium can be further mitigated by avoiding PP while following established best practices should be the topic of further research.

ORCID

Somnath Bose https://orcid.org/0000-0001-7310-9881
Lauren Kelly https://orcid.org/0000-0003-0544-800X
Zachary Shahn https://orcid.org/0000-0003-1014-8837
Lena Novack https://orcid.org/0000-0003-3748-2632
Valerie Banner-Goodspeed https://orcid.org/0000-0002-7644-2521
Balachundhar Subramaniam https://orcid.org/0000-0001-6510-3885

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SUPPORTING INFORMATION

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