Association of sedation, coma, and in-hospital mortality in mechanically ventilated patients with COVID-19 related acute respiratory distress syndrome: A retrospective cohort study.

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Supplementary document

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In order to respect space limitation in the main manuscript, we present further information on methods and results in this supplementary document.

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Section 1. Data sources

Demographic data including age, race, sex and body mass index (BMI) as well as information on the patient's health status prior to admission (past medical history, Charlson comorbidity index (CCI)) were collected from online medical records. Laboratory values and ICU-specific data, such as physiologic variables, level of consciousness, ventilatory parameters, laboratory values, and administered medications were retrieved from Metavision, an interface that is routinely used for all ICUs in our hospital network. Encounter dates, admission source and discharge disposition information were retrieved from Casemix and the Admission Discharge Transfer database. Radiographic imaging reports were obtained from the radiology database.

Section 2. Outcome variables

2.1 Sedation burden index (SBI)

To calculate the SBI, the drug dose administered to each individual patient was divided by the drug dose administered plus the minimum recommended daily dose during every day of mechanical ventilation ($SBI = \sum \frac{D}{d+D}$ where *D* is the administered drug dose, and *d* is a minimum recommended daily dose) (1–3).

For example, if 31.2 mg/kg propofol and 0.24 mg/kg midazolam have been administered to a patient during the first mechanical ventilation day, the SBI on this first mechanical ventilation day of this patient would have been

$= \frac{31.26}{7.2+31.26} + \frac{0.24}{0.48+0.24}$

= 0.81 + 0.33

= 1.14

The minimum recommended daily dose is provided in *eTable 4* (3).

The average SBI during the mechanical ventilation over a 10-day period wascalculated for each patient. We then identified the maximum achieved SBI over the first 10 days of mechanical ventilation with an index value of 3.29. Any individual value of average SBI was expressed as the percentage of the maximum value. To compare the cumulative burden of sedatives between the COVID-19 and non-COVID-19 patients, the mean percent of individualized values were compared between the two groups.

Section 3. Propensity score matching

We created the propensity score using a logistic regression model with COVID-19 infection as the dependent variable and a priori selected covariates representing the probability that affect the exposure (COVID-19 ARDS) and affect the outcome (in-hospital mortality); age, sex, body mass index, Charlson comorbidity index, Acute Physiology and Chronic Health Evaluation (APACHE) II score, present of renal impairment (serum creatinine ≥2.5), present of severe liver injury (total bilirubin ≥5 mg/dL and INR ≥1.5), vasopressor support (mg of norepinephrine equivalents), respiratory system compliance, P_aO_2:F_IO_2-ratio, P_aCO_2, and A-a gradient as independent variables (1–3). Based on a propensity score built based on the described covariates, we matched patients using a greedy algorithm without replacement. Matched pairs (COVID-19 and non-COVID-19 patient) were identified within a closeness range of 0.00001 of the propensity score first and then if no more individuals can be found, the program identifies matched pairs in a range of 0.0001 etc., up to a closeness range of 0.1. Patients were matched up to 1:2. The effectiveness of matching was evaluated by calculating weighted conditional standardized differences of covariates after propensity score adjustment (*Table 1*). Covariates with weighted conditional standardized differences above 0.1 were added to the confounder model in the following analyses.

Section 4. Sensitivity and exploratory analyses

4.1 Additional adjustment for respiratory drive

COVID-19 patients had a lower baseline minute ventilation (8.7 (7.7, 10) versus 9.2 (7.7, 10) L/min) and a higher pH (7.34 [7.27, 7.38] versus 7.29 [7.19, 7.36] [p<0.001, *Table 1*]). The result was confirmed when adjusting for respiratory drive (minute ventilation and pH). COVID-19 patients experienced a higher percentage of coma (adjusted coefficient [aCoef] 33.91; 95%CI 25.97-41.85; p<0.001), which in turn was significantly associated with in-hospital mortality (adjusted OR [aOR] 2.66; 95%CI 1.61-4.37; p<0.001). The effect of COVID-19 on in-hospital mortality was mediated through the indirect effect of coma (p<0.001).

4.2 Additional adjustment for ARDS severity

In a sensitivity analysis, we adjusted for ARDS severity (by using oxygenation criteria from the Berlin definition (4)) instead of using P/F ratio as a confounder in the primary model. This analysis confirmed our primary findings: Patients with COVID-19 experienced a higher percentage of coma (aCoef 34.01; 95%CI 30.44-37.58; p<0.001), which in turn was significantly associated with in-hospital mortality (aOR 5.84; 95%CI 3.56-9.58; p<0.001). 58.6% of the effect of COVID-19 on in-hospital mortality was mediated through the effect of coma (p<0.001).

4.3 Additional adjustment for prone position

To account for different treatment modalities, prone positioning was included as a confounder in the sensitivity analysis. The result was confirmed that COVID-19 patients experienced a higher percentage of coma (aCoef 18.87; 95%CI 9.68-28.06; p<0.001), which in turn was significantly

associated with in-hospital mortality (aOR 2.81; 95%CI 1.73-4.58; p<0.001). The effect of COVID-19 on in-hospital mortality was mediated through the indirect effect of coma (p<0.001).

4.4 Additional adjustment for NMBA infusions

To account for different treatment modalities, the use of NMBA infusions was included as a confounder in a sensitivity analysis. This analysis confirmed that COVID-19 patients experienced a higher percentage of coma (aCoef 17.29; 95%CI 9.95-24.64; p<0.001), which in turn was significantly associated with in-hospital mortality (aOR 2.39; 95%CI 1.43-3.99; p=0.001). The effect of COVID-19 on in-hospital mortality was mediated through the indirect effect of coma (p<0.001).

4.5 Additional adjustment for daily SOFA score

To account for the change in acuity of illness over time, the daily Sequential Organ Failure Assessment (SOFA) scores were calculated at day 1, 2, and 3 (D1, D2 and D3) after start of mechanical ventilation, and its change from day 1-3 was included as a confounder variable, as previously published (4, 5). The result was confirmed that COVID-19 patients experienced a higher percentage of coma (aCoef 26.43; 95%CI 18.57-34.28; p<0.001), which in turn was significantly associated with in-hospital mortality (aOR 2.68; 95%CI 1.64-4.38; p<0.001). The association between COVID-19 and in-hospital mortality was still robust (aOR 2.03; 95%CI 1.26-3.27; p=0.004).

4.6 Additional adjustment for delirium

Deeper sedation should result in a high risk of delirium, which was confirmed in our study (delirium free days: 10 [IQR 1–19] days in patients with COVID-19 versus 20 [IQR 3–25] days in patients with non-COVID-19). We considered to add delirium (defined as CAM-ICU positive on any day during mechanical ventilation (6)) to the primary model. The adjusted analysis with additional adjustment for delirium as a confounder demonstrated that COVID-19 patients experienced a higher percentage of coma during the first 10 days of mechanical ventilation (aCoef 25.51; 95%CI 17.76-33.26; p<0.001), which in turn was significantly associated with in-hospital mortality (aOR 2.96; 95%CI 1.58-5.02; p<0.001). The association between COVID-19 and in-hospital mortality was still robust (aOR 1.81; 95%CI 1.09-3.00; p=0.022).

4.7 Analyses using a re-categorized mediator variable

To address potential bias related to the ascertainment of the mediator variable, we re-categorized the definition of coma by using a RASS of -4 or -5, which revealed a similar association of COVID versus non-COVID-related ARDS and coma (7). COVID-19 patients experienced a higher percentage of coma during the first 10 days of mechanical ventilation (49.3±36.2%) compared with non-COVID-19 patients (24.1±33.0%). This result was confirmed in an adjusted analysis (aCoef 24.77; 95%CI 17.13-32.41; p<0.001). In addition, the effect of COVID-19 on in-hospital mortality was also mediated through the indirect effect of coma (aOR 1.42; 95%CI 1.16-1.73; p=0.001).

4.8 Analyses of 30-day mortality

We re-defined the outcome as 30-day mortality, and the unique associations of COVID-19, deep sedation, coma, and mortality remained robust. Patients with COVID-19-related ARDS experienced a higher percentage of coma (aCoef 29.34; 95%CI 21.45-37.24; p<0.001), which in turn was significantly associated with 30-day mortality (aOR 6.19; 95%CI 3.75-10.22; p<0.001). The effect of COVID-19 on 30-day mortality was mediated through the indirect effect of coma (aOR 1.60; 95%CI 1.29-1.99; p<0.001).

A time-to-event analysis to examine differences in mortality during 30 days after ICU admission is provided as *eFigure 5*.

4.9 Readmission to the ICU

Patients are can be transferred to the floor, decompensate, and are then transferred back to the ICU where they may experience coma again and also may die. In order to address this potential bias, we included the percentage of deep sedation during the stay after readmission to the ICU. Twelve patients (10 patients with non-COVID-19, 2 patients with COVID-19) were readmitted to the ICU within 30 days after the index stay. Using this modified variable, COVID-19 patients experienced a higher percentage of coma (aCoef 29.19; 95%CI 21.28-37.09; p<0.001), which in turn was significantly associated with 30-day mortality (aOR 6.19; 95%CI 3.75-10.22; p<0.001). The effect of COVID-19 on 30-day mortality was mediated through the indirect effect of coma (p<0.001). In addition, we also added the readmission to the ICU as a confounder to model, which did not affect our described, unique associations.

4.10 Intra-group analyses

To address potential concerns that COVID-19 versus non-COVID-19 status cannot be blinded, we performed intra-group analyses on the association between level of sedation and in-hospital mortality. The association between a higher percentage of coma and in-hospital mortality could be demonstrated in both COVID-19 (aOR 3.84; 95%CI 1.69-8.71; p=0.001) and non-COVID-19 (aOR 3.07; 95%CI 1.66-5.65; p<0.001) patients.

4.11 Subgroup of non-COVID-19 patients with established microbiology reports

We compared non-COVID-19 patients with established microbiology reports with COVID-19 patients and assessed the effect on percentage of coma, and in-hospital mortality as well as the mediating effect of coma on mortality. The subgroup analyses in non-COVID-19 patients with established microbiology reports (36.4%; n=83) compared with COVID-19 patients revealed that COVID-19 patients experienced a higher percentage of coma (aCoef 27.81; 95%CI 17.97–37.65; p<0.001), which in turn was significantly associated with in-hospital mortality (aOR 4.46; 95%CI 2.33-8.53; p<0.001). The effect of COVID-19 on in-hospital mortality was mediated through the indirect effect of coma (p=0.003)

4.12 Analyses in the full cohort of patients with the diagnosis of ARDS

In the primary analysis, we matched for possible predictors of the exposure and outcome (8). In order to address a potential selection bias, we repeated the analysis using the same covariate model in the complete, unselected cohort of all ARDS patients. In the complete, unselected cohort of all ARDS patients (n=3,201; *eTable 1*), COVID-19 patients experienced a higher percentage of coma (aCoef 35.00; 95%CI 29.25-40.70; p<0.001), which in turn was significantly associated with in-

hospital mortality (aOR 3.57; 95%CI 2.97-4.30; p<0.001). The effect of COVID-19 on in-hospital mortality was mediated through the indirect effect of coma (p<0.001).

4.13 Daily variability in physiologic variables

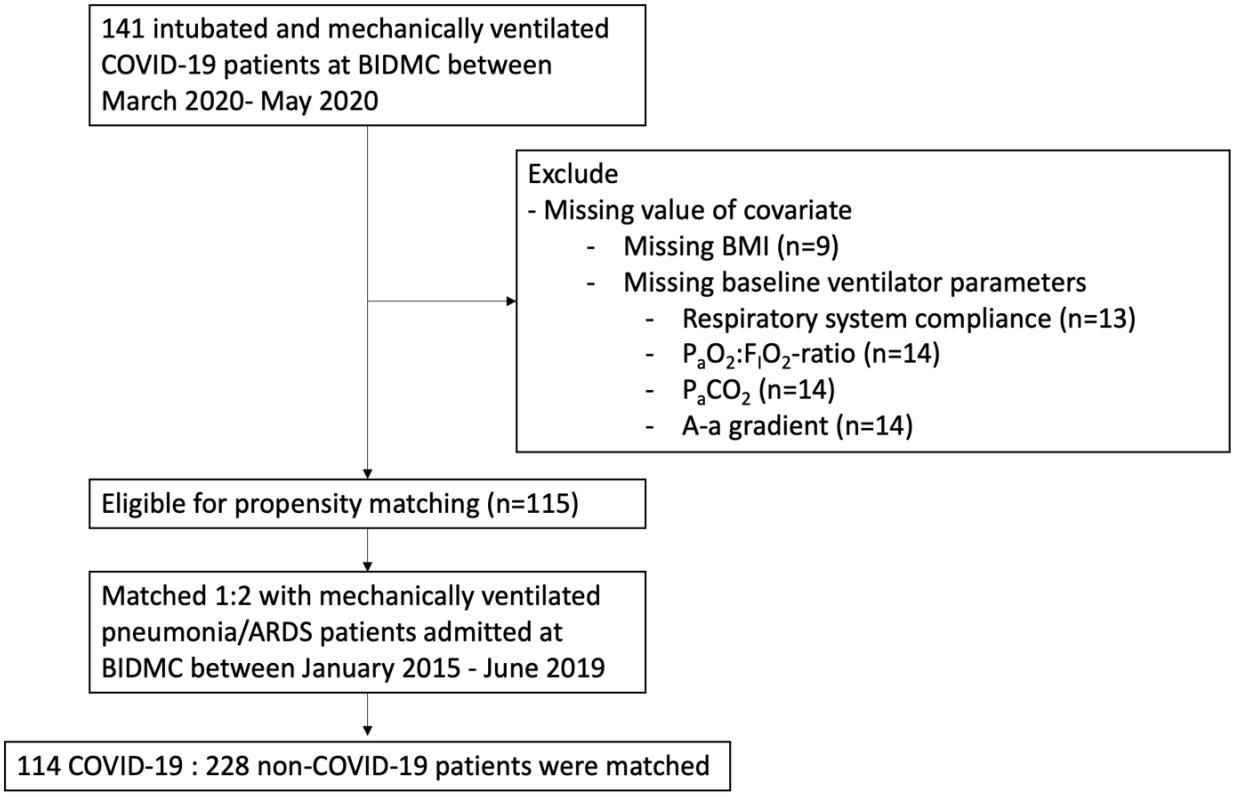
Daily variability in physiologic parameters (F_IO_2, tidal volume, respiratory rate and RASS) during the first 10 days of mechanical ventilation were assessed to better understand the factors that influenced the use of high doses of sedative medications. First, we calculated the mean value of the parameter of an individual patient for each day. Second, we assessed the variability by calculating the difference between each parameter measured and the mean value of each individual patient. Finally, the mean variability of individual patients on each day was compared between COVID-19 and non-COVID-19 patients using chi-square statistics.

Daily variabilities in COVID-19 and non-COVID-19 patients across patients and in patients with RASS ≥-1 are provided in *eFigure 6* and *eFigure 7*. The highest F_IO_2 variability was found during the first 2 days of mechanical ventilation (about 4-6% F_IO_2) in both COVID-19 and non-COVID-19 patients. The daily mean variability in F_IO_2 was not significantly different during the first 10 days of mechanical ventilation. Daily tidal volume and RASS variabilities were higher in non-COVID-19 patients.

Section 5. Figures and tables

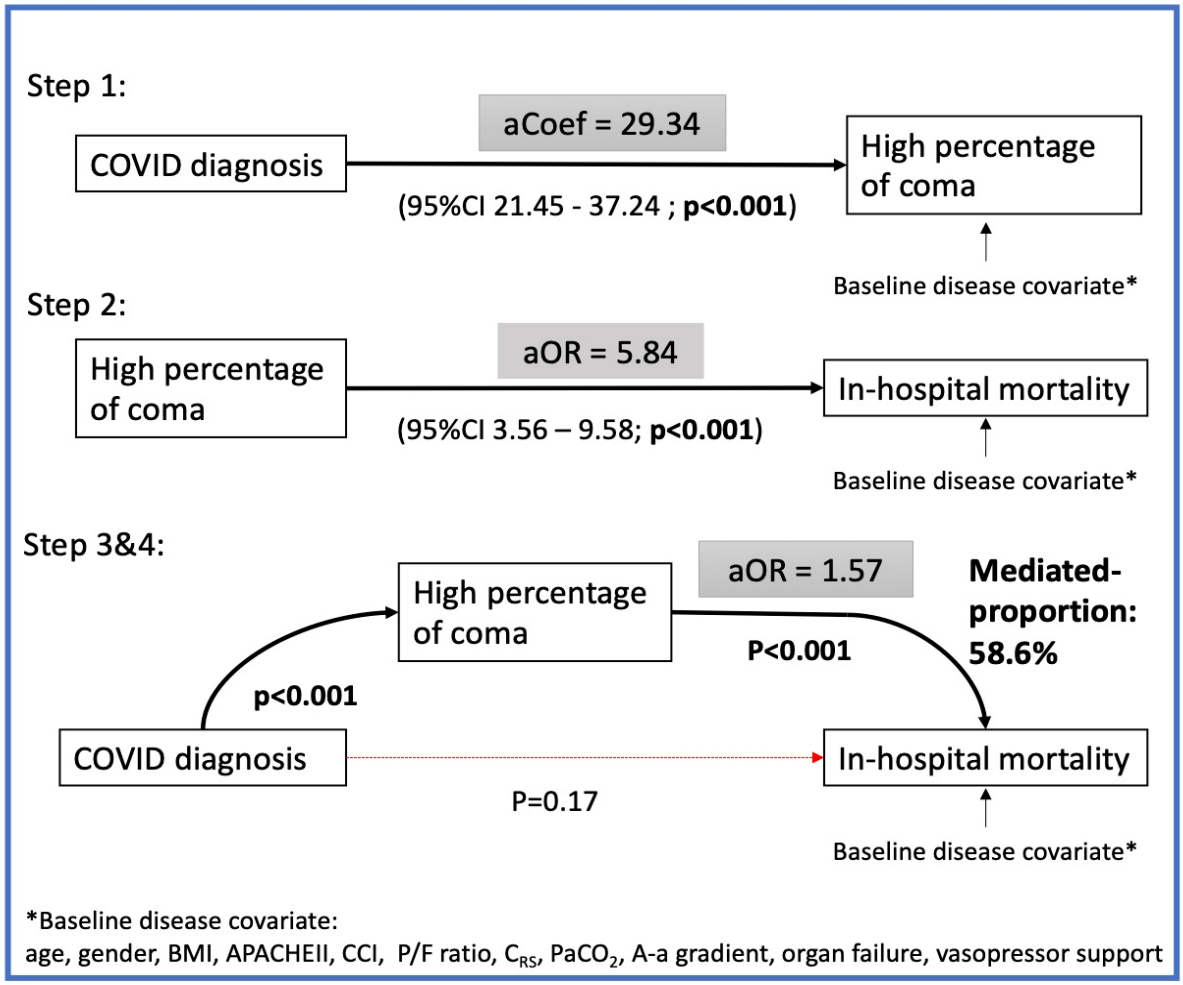
eFigure 1. Study flow

BIDMC, Beth Israel Deaconess Medical Center; BMI, body mass index; P_aO_2:F_IO_2-ratio, arterial partial pressure of oxygen/the fraction of inspired oxygen ratio; P_aCO_2, arterial partial pressure of carbon dioxide; A-a gradient, alveolar-arterial gradient.



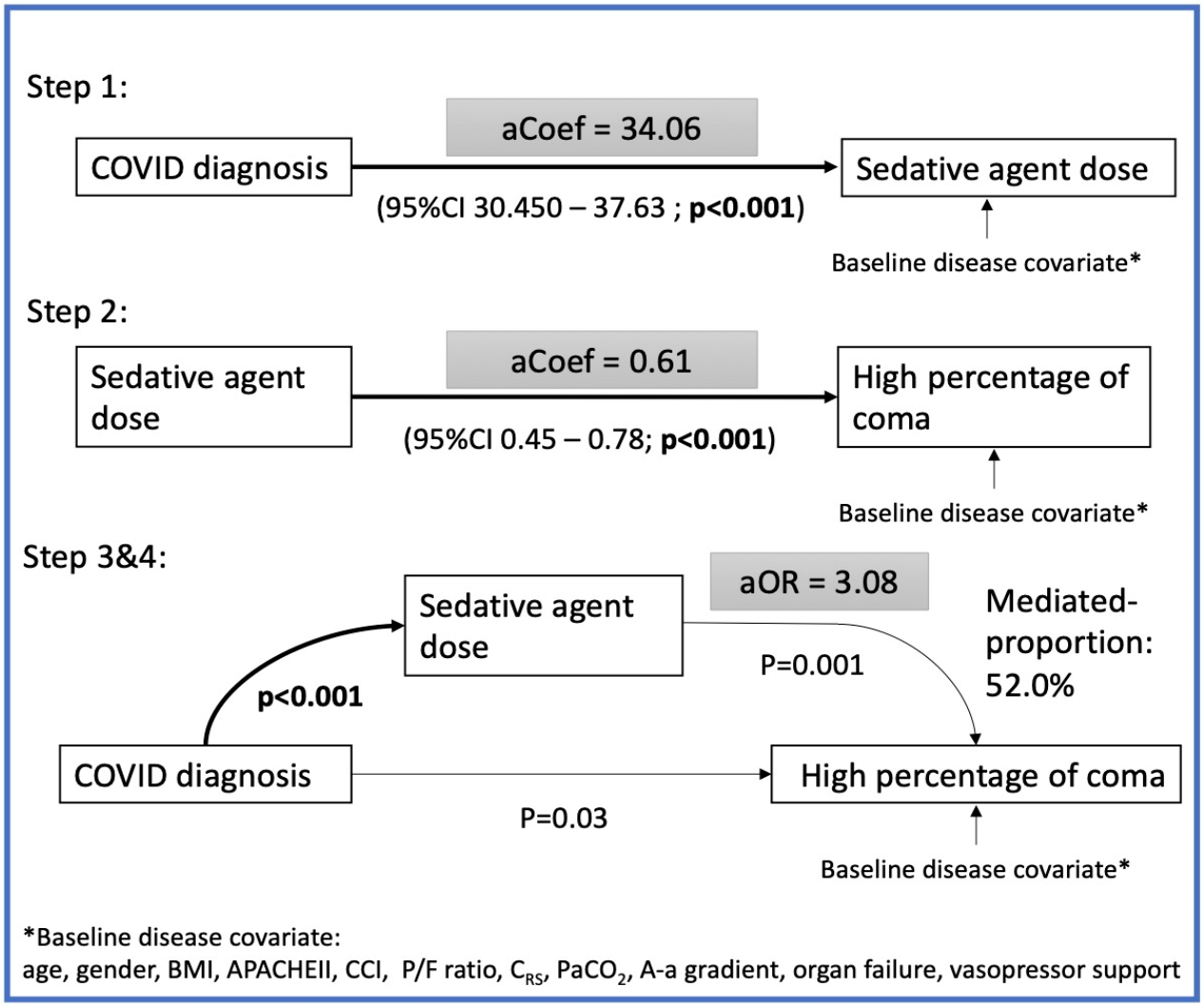
eFigure 2. Mediation analysis of a high percentage of coma as a mediator in the primary association between COVID-19 and in-hospital mortality

First, we demonstrated that COVID-19 patients had a higher percentage of coma. Second, we assessed whether the potential mediator (high percentage of coma) was associated with in-hospital mortality. Finally, a mediation analysis (Step 3&4) was used to calculate the influence of COVID-19 diagnosis on the percentage of coma and the influence of a high percentage of coma on in-hospital mortality. Solid arrows in the path diagram present significant association between variables, with left to right direction representing an independent to dependent relationship. Red dashed arrows represent non-significant effects.



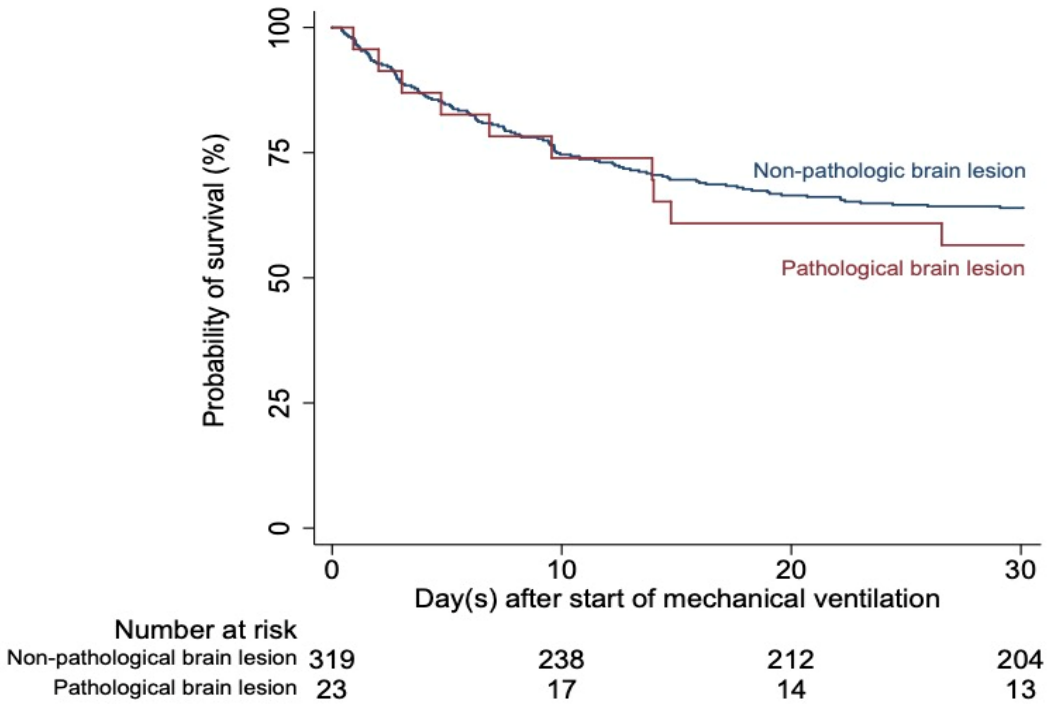
eFigure 3. Mediation analysis of sedation agent dose as a mediator in the secondary association between COVID-19 and coma

First, we demonstrated that COVID-19 patients received a higher sedation agent dose. Second, we assessed whether the potential mediator (sedative agent dose) was associated with coma. Finally, a mediation analysis (Step 3&4) calculated the influence of COVID-19 diagnosis on the sedative agent dose and of the sedative agent dose on coma. Solid arrows in the path diagram present significant association between variables, with left to right direction representing an independent to dependent relationship. Red dashed arrows represent non-significant effects.



eFigure 4. Cox proportional hazards regression analysis

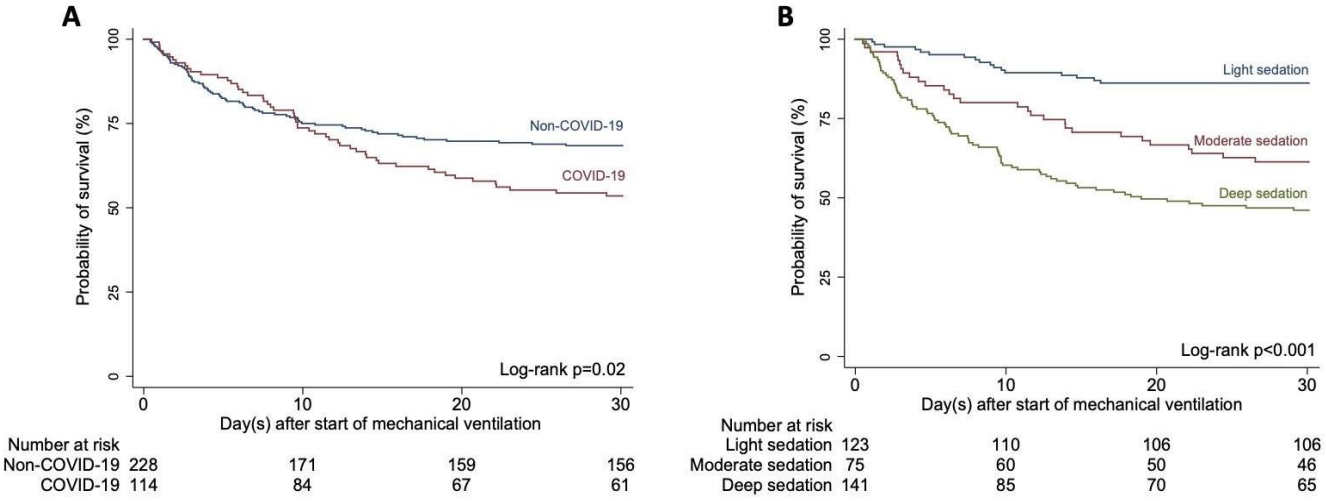
Kaplan-Meier curves for the probability of survival up to day 30 after start mechanical ventilation are shown for different causes of coma (sedation-related coma [Non-pathologic brain lesion, blue line] versus neurologic injury-related coma [Pathological brain lesion, red line]). The proportional hazards ratio was not significant compared between sedation-related coma versus neurologic injury-related coma (adjusted hazard ratio 1.34; 95%CI 0.69-2.59; p=0.38).



eFigure 5. Time-to-event analysis for 30-day mortality

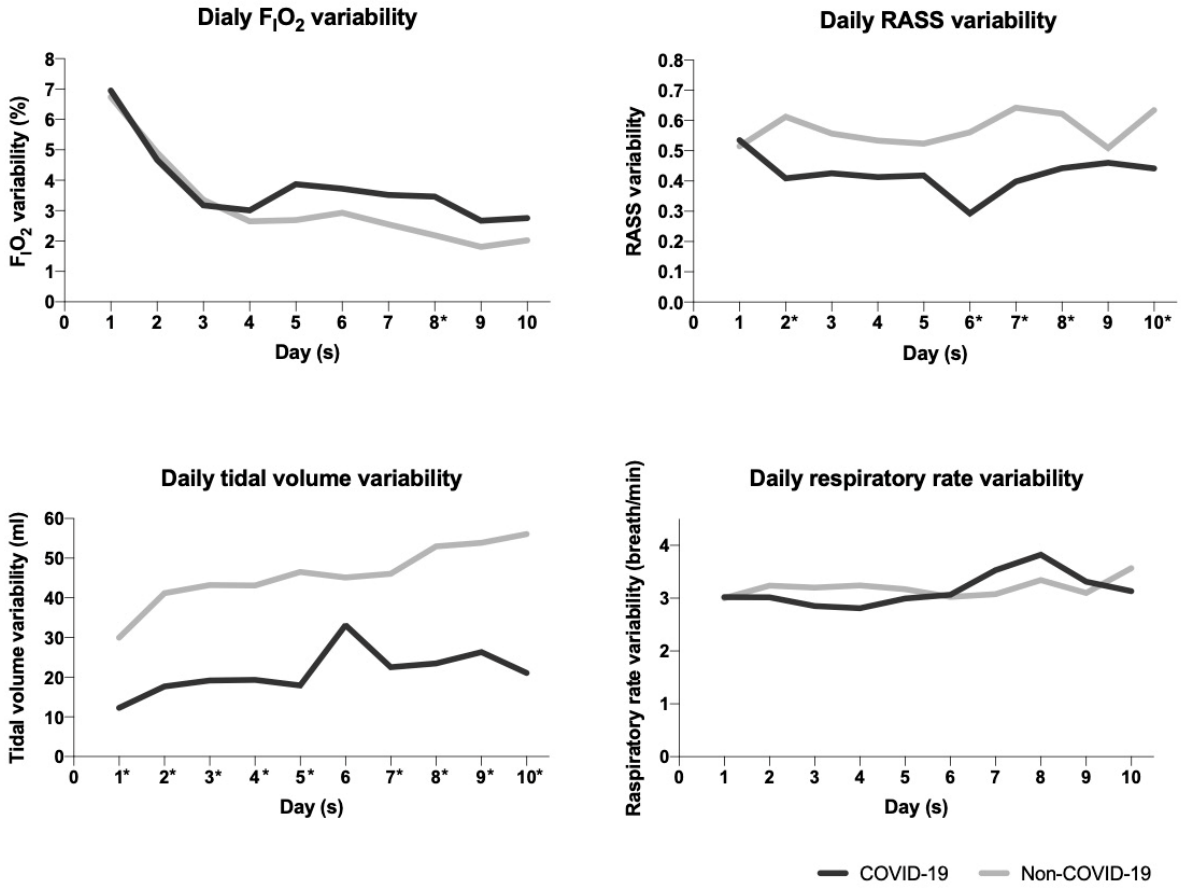
Panel A: Kaplan-Meier curves for the probability of survival up to day 30 after the start of mechanical ventilation are shown for COVID-19 and non-COVID-19 patients. A reduced probability of survival in COVID-19 patients can be demonstrated (log-rank p=0.02).

Panel B: Kaplan-Meier curves for the probability of survival up to day 30 after the start of mechanical ventilation are shown for different sedation regimens. Sedation levels were categorized into light (RASS ≥-2), moderate (RASS =-3), and deep (RASS ≤-4), based on the highest percentage of sedation recorded during the first 10 days after start mechanical ventilation. Data from patients discharged before day 30 were censored at day 30, with the patients considered to be alive at day 30. Deeper sedation was associated with a significantly reduced survival (log-rank p<0.001).



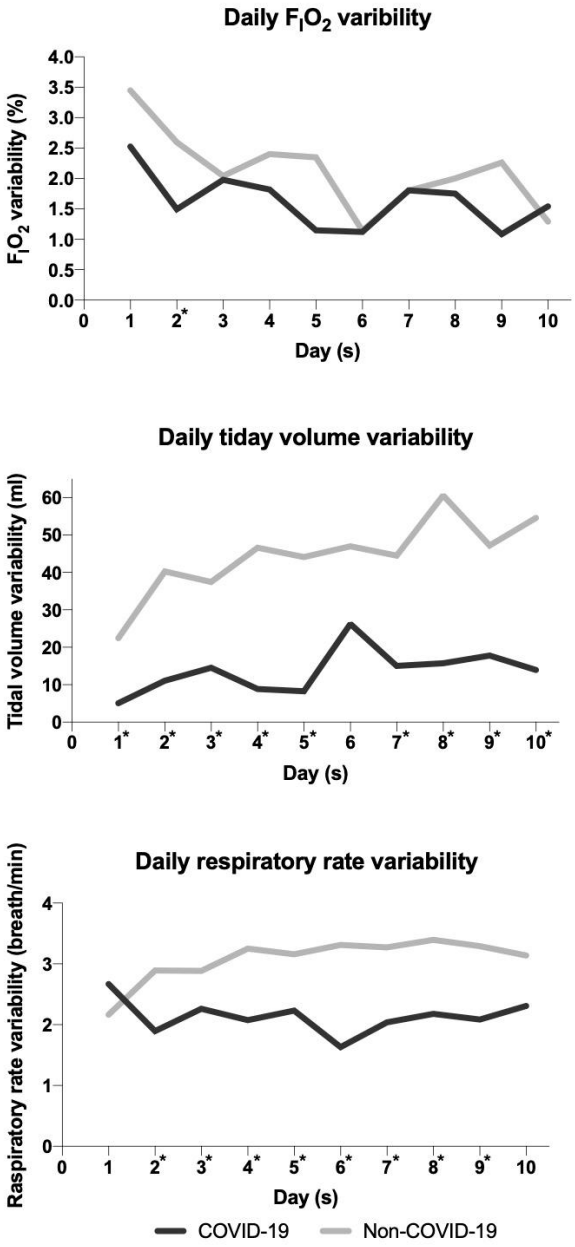
eFigure 6. Daily variability in physiologic variables during the first 10 days of mechanical ventilation

Daily variability for F_IO_2, Richmond agitation sedation score (RASS), tidal volume, and respiratory rate was calculated as the average of the difference between variable measured and daily mean value for each individual patient. *p<0.05.



eFigure 7. Daily variability in physiologic variables during the first 10 days of mechanical ventilation in patients with Richmond agitation sedation score (RASS) ≥-1

Daily variability for F_IO_2, tidal volume, and respiratory rate was calculated as the average of the difference between variable measured and daily mean variable in patients with RASS ≥-1. *p<0.05.



eTable 1. Baseline characteristics at the time of start mechanical ventilation by COVID diagnosis

Characteristics	**Non-COVID-19 in ARDS cohort (n=3087)**	**Non-COVID-19 in matched cohort (n=228)**	**COVID-19 (n=114)**	**Standardized differences**
Age (yr)	60.8 ± 16.8	62.3 ± 17.2	60.6 ± 15.9	-0.024
Female sex; n (%)	1271 (41%)	115 (50.4)	53 (47)	-0.044
Body mass index (kg/m^2)	28.4 (24.2, 34.1)	29.8 (24.8, 36.2)	30.8 (27.3, 36.2)	0.011
APACHE II	23 (18, 27)	25 (20, 30)	24 (20, 29)	-0.006
Charlson Comorbidity Index	0 (0, 4)	0 (0, 2.5)	0 (0, 2)	0.027
Respiratory system compliance (ml/cmH_2O)	45.4 ± 39.4	40.7 ± 18.6	39.9 ± 21.8	-0.118
PaO_2: F_IO_2 - ratio	168 (121, 224)	164 (109, 288)	174 (117, 270)	0.012
$PaCO_2$ (mmHg)	44.4 ± 12.7	48.6 ± 16.3	47.8 ± 13.2	0.017
A-a gradient	260 (206, 413)	435 (256, 557)	427 (265, 534)	0.040
Creatinine	1.7 ± 1.5	1.6 ± 1.3	1.5 ± 1.3	0.019
Total bilirubin (mg/dL)	2.5 ± 5.4	1.6 ± 1.4	1.7 ± 1.5	-0.288
INR	1.7 ± 1.0	1.4 ± 3.3	0.7 ± 1.0	-0.105
Vasopressor (mcg of norepinephrine equivalents)	0.009 ± 0.018	0.052 ± 0.177	0.043 ± 0.133	-0.080
pH	7.35	7.28	7.34	0.149

	(7.27, 7.41)	(7.18, 7.36)	(7.27, 7.38)	
Glasgow Coma Scale	9 (8, 15)	8 (8, 14)	8.5 (8, 15)	0.133
Renal impairment; n (%)	585 (19.0)	31 (13.6)	15 (13.2)	-0.045
Severe liver injury; n (%)	541 (17.5)	6 (2.6)	3 (2.6)	-0.090
ARDS severity; n (%)				-0.066
Mild	1019 (33.5)	88 (38.6)	44 (38.6)	
Moderate	1531 (50.3)	91 (39.9)	51 (44.7)	
Severe	493 (16.2)	49 (21.5)	19 (16.7)	

Data are presented as n (%), mean ± standard deviation, or median (interquartile range).

Renal impairment defined as creatinine level ≥ 2.5 mg/dL.

Severe liver injury defined as total bilirubin ≥ 5 mg/dL and INR ≥ 1.5.

APACHE II: Acute Physiology and Chronic Health Evaluation II score; $P_aO2:F_IO_2$-ratio: Arterial partial pressure of oxygen/the fraction of inspired oxygen ratio; $PaCO_2$: Arterial partial pressure of carbon dioxide.

eTable 2. Daily sedation parameters during the first 10 days of mechanical ventilation

Day of mechanical ventilation	Non-COVID-19		COVID-19	
	Mean ± SD	**Variance**	**Mean ± SD**	**Variance**
Day 1	-3.2 ± 1.6	1.3 ± 3.9	-3.5 ± 1.3	2.0 ± 5.9
Day 2	-2.9 ± 1.7	1.1 ± 2.7	-3.9 ± 1.1	0.7 ± 1.5
Day 3	-2.6 ± 1.7	0.9 ± 2.0	-3.8 ± 1.3	0.4 ± 1.1
Day 4	-2.5 ± 1.7	0.9 ± 2.8	-3.7 ± 1.4	0.6 ± 2.1
Day 5	-2.4 ± 1.7	0.9 ± 3.0	-3.7 ±1.4	0.5 ± 1.2
Day 6	-2.2 ± 1.8	0.5 ± 1.0	-3.8 ± 1.4	0.3 ± 0.6
Day 7	-1.9 ± 1.8	1.0 ± 2.3	-3.5 ± 1.6	0.4 ± 1.1
Day 8	-1.9 ± 1.8	1.3 ± 3.6	-3.4 ± 1.7	0.5 ± 1.0
Day 9	-1.9 ± 1.8	0.6 ± 1.2	-3.2 ± 1.7	0.5 ± 1.4
Day 10	-1.8 ± 1.8	0.7 ± 1.2	-3.2 ± 1.6	0.4 ± 0.9

Data are expressed as mean ± standard deviation.

eTable 3. Number and duration of sedatives, analgesics and neuromuscular blocking agent treatment during mechanical ventilation

Drugs administered	Number of treatments			Duration of treatment		
	Non-COVID (n=228)	COVID (n=114)	p-value	Non-COVID (n=228)	COVID (n=114)	p-value
Opioids (oral morphine equivalents)	214 (93.9%)	112 (98.2%)	0.07	5.6 ± 4.7	10.1 ± 5.7	<0.001
Propofol	201 (88.2%)	111 (97.4%)	0.005	3.9 ± 2.8	7.4 ± 5.0	<0.001
Midazolam	120 (52.6%)	83 (72.8%)	<0.001	2.8 ± 2.7	6.3 ± 4.4	<0.001
Lorazepam	42 (18.4%)	23 (20.2%)	0.7	1.5 ± 1.1	1.5 ± 1.1	0.93
Diazepam	1 (0.4%)	12 (10.5%)	<0.001	2	3.9 ± 3.0	0.55
Dexmedetomidine	102 (44.7%)	65 (57.0%)	<0.001	3.8 ± 2.9	5.1 ± 3.5	0.010
Ketamine	2 (0.9%)	59 (51.8%)	0.032	1.5 ± 2.9	7.4 ± 4.5	0.072
Neuromuscular blocking agents	53 (23.2%)	64 (56.1%)	<0.001	2.6 ± 2.4	4.8 ± 3.9	<0.001

Data are expressed as n (%) and mean ± standard deviation.

eTable 4. Lowest daily recommended dose of sedative and analgesic drugs

Drugs	**Lowest recommended infusion dose***	**Lowest daily recommended dose**
Fentanyl	0.7 mcg/kg/hr	16.8 mcg/kg/d
Hydromorphone	0.5 mg/hr	12 mg/d
Morphine	2 mg/hr	48 mg/d
Methadone	2.5 mg q 8 hr	7.5 mg/d
Remifentanil	0.5 mcg/kg/hr	12 mcg/kg/d
Ketamine	0.05 mg/kg/hr	1.2 mg/kg/d
Midazolam	0.02 mg/kg/hr	0.48 mg/kg/d
Lorazepam	0.01 mg/kg/hr	0.24 mg/kg/d
Diazepam	0.03 mg/kg q 0.5 hr	1.44 mg/kg/d
Propofol	5 mcg/kg/min	7.2 mg/kg/d
Dexmedetomidine	0.2 mcg/kg/hr	4.8 mcg/kg/d

* Lowest recommended infusion dose according to Barr J, et al. (Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306.)

eTable 5. Effect modification and subgroup analyses on the mean percent maximum of SBI

Effect modifier	Predicted mean % maximum of SBI		Adjusted coefficient (95% CI)	p-value
	COVID-19 (n=114)	Non-COVID-19 (n=228)		
Prone position			**p for interaction 0.04**	
Prone (n = 63)	61.5 (57.6, 65.4)	24.5 (14.3, 34.7)	37.0 (26.1, 47.9)	< 0.001
Non-prone (n = 279)	41.6 (37.8, 45.4)	16.9 (14.9, 18.8)	24.7 (20.5, 29.0)	< 0.001
Neuromuscular blocking agents			**p for interaction 0.121**	
NMBA infusion (n = 117)	58.3 (54.7, 62.0)	25.0 (21.0, 29.1)	33.3 (27.9, 38.6)	<0.001
No-NMBA infusion (n = 225)	42.3 (38.2, 46.4)	14.7 (12.5, 16.9)	27.6 (23.0, 32.3)	<0.001

For analyses of effect modification, interaction terms between COVID-19 dichotomized variables were included separately into the secondary regression model for the secondary outcome of the mean percent maximum of SBI. Linear combinations of the respective main effect and interaction term were performed to assess the association between exposure and outcome across different subgroups. Results are reported as adjusted coefficient for a COVID-19 patient.

Section 6. References

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