ORIGINAL ARTICLE

Sedation Practices for Intubated Patients with COVID-19 and non-COVID-19 Acute Respiratory Distress Syndrome and its Effects on Clinical Outcomes

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ABSTRACT

Objective. To compare the sedation practices of adult intubated patients with COVID-19-related Acute Respiratory Distress Syndrome (C-ARDS) and ARDS from other causes, and their impact on clinical outcomes in a tertiary hospital.

Methods. We performed a retrospective cohort on the sedation practices of adult intubated patients with C-ARDS and non-C-ARDS admitted to the intensive care unit of a tertiary hospital from January 2021 to December 2021. Electronic medical records were reviewed to obtain sedative use, sedative dosages, clinical outcomes, and complications.

Results. Among the 150 included patients, 112 had C-ARDS, and 38 had non-C-ARDS. The C-ARDS group showed a significant difference with the non-C-ARDS group in terms of BMI (24.11 vs. 21.09 kg/m^2, p<0.001), use of higher PEEP (16 vs. 10, p<0.001), and prone positioning (40.18% vs 2.63%, p<0.01). In terms of sedation practice, C-ARDS patients targeted deeper RASS scores (p=0.038), with a significantly higher proportion receiving more than one sedative (82.14% vs. 18.42, p<0.001) than non-C-ARDS patients. Sedation doses for midazolam (78 mg/d vs. 36 mg/d; p=0.01) and propofol (mean 2626±1312.97 mg/d vs. 1742±380.99 mg/d; p=0.007), were significantly higher among C-ARDS versus non-C-ARDS group. Duration of hospitalization (9 vs. 20 days; p<0.001) and ventilator use (7 vs. 14.50 days; p<0.001) were significantly shorter in the C-ARDS group, albeit with a high mortality (100% vs. 89.47%; p=0.004). Shock-requiring pressor was significantly associated with multiple sedation use [OR=15.11 (1.52-2032.89); p=0.017] and combination use of benzodiazepine and non-benzodiazepines [OR=11.51 (1.17-1541.91); p=0.034] in the C-ARDS but not the C-ARDS group.

Conclusion. Patients with C-ARDS had higher sedation requirements in terms of dosage and number of sedatives. The use of multiple sedatives was significantly associated with shock-requiring pressor. We recommend the development of a sedation protocol to guide sedation practices and monitoring of complications in the critically ill.

Keywords: COVID-19, ARDS, sedation practices, intensive care, sedative

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INTRODUCTION

Sedation is a routine supportive measure among critically ill intubated patients, including those with acute lung injuries or acute respiratory distress syndrome (ARDS).[1] Aside from optimizing patient care and comfort, sedation improves gas exchange and promotes ventilator synchrony.[2] Patients may be placed in deep sedation as advanced ventilation support is utilized to target hypoxemic respiratory failure.

The most commonly used sedative classes in mechanically ventilated patients admitted to the intensive care unit (ICU) include benzodiazepines (diazepam, lorazepam, or midazolam), GABAA receptor agonist (propofol), α2-adrenergic receptor agonists (clonidine or dexmedetomidine), NMDA receptor agonist (ketamine), and inhalation anesthetics as monotherapy or in combination.[1,3] Although these sedative agents carry a similar mortality risk in ICU patients, α2-adrenergic receptor agonists and benzodiazepines, alone or in combination with propofol and ketamine, are associated with more extended ICU stay compared to propofol monotherapy.[3] However, some studies indicate that benzodiazepines may be associated with a higher rate of in-hospital mortality and one-year mortality among patients requiring over 48 hours of mechanical ventilation.[4] In addition, benzodiazepines are associated with an increased risk of delirium compared to α2-adrenergic receptor agonists or propofol.[3] Non-benzodiazepines like dexmedetomidine have been associated with a lower risk of delirium and shorter duration of mechanical ventilation and ICU stay compared to other sedatives, albeit with increased risks of bradycardia and hypotension.[5]

Regardless, deep and prolonged sedation is not without its drawbacks. As indicated above, complications can include delirium, withdrawal syndromes, hemodynamic instability, and prolonged weaning and ICU stay.[6] Although the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep (PADIS) guidelines recommend the use of sedatives in critically ill patients to relieve anxiety and prevent agitation-related harm, it also recommends using light sedation to improve short-term outcomes such as time of extubation and length of ICU stay.[7]

During the recent COVID-19 pandemic, several studies noted that patients with COVID-19 ARDS (C-ARDS) had an unusually high sedative dose requirement than non-C-ARDS patients, usually exceeding the upper recommended limit, therefore necessitating the co-administration of two or more agents to achieve adequate sedation.[6,8-12] For instance, a study by Wongtangman et al.[13] showed that C-ARDS patients received substantially higher doses of sedatives with longer treatment duration than patients with ARDS of other etiology. Moreover, Tapaskar et al.[8] demonstrated that C-ARDS patients required cumulative doses of both benzodiazepine and non-benzodiazepine sedatives to achieve an equivalent Richmond Agitation-Sedation Scale (RASS) score compared to non-C-ARDS patients.[8] These patients also required longer ventilator days.[8] The need to administer multiple agents has been related to the patients' high respiratory drive and intense inflammatory responses.[6] These maneuvers achieve ventilator synchrony despite high positive end-expiratory pressure (PEEP), advanced ventilation support, and prone positioning.[13] However, deep and prolonged sedation of patients with C-ARDS has been shown to lead to a higher percentage of coma and in-hospital mortality.[13]

Despite the risk of severe adverse effects due to high sedative use, no current guideline exists for COVID-19 patients. Limited studies have identified patients' clinical outcomes based on the difference in sedation practices. Therefore, the goal of this study is to consolidate information on sedation practices from a tertiary hospital, the main COVID referral center in the Philippines, among patients with C-ARDS and ARDS from other etiology and determine its impact on clinical outcomes such as mortality, length of hospital stay, duration of ventilation, time to extubation, and complications such as hypotension and delirium.

METHODS

Study Design and Setting

This retrospective cohort analytical study involved adult patients diagnosed with ARDS admitted to the Philippine General Hospital from January 2021 to December 2021. December 31, 2021 was considered the last date for eligibility. The study commenced upon the approval of the Institutional Review Board of Philippine General Hospital (UPMREB 2022-0434-01). A waiver of informed consent was requested from the UPMREB panel in line with the National Ethical Guidelines of Health and Health-related Research 2017 since (1) the research presents no more than minimal risk, and (2) the waiver or alteration will not adversely affect the rights and welfare of the participants.

Study Participants

The medical records of all patients admitted to the ICU during the study period were accessed through electronic records (census, Computerized Registry of Admissions and Discharges). Only adult intubated patients diagnosed with ARDS based on history, imaging, and arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO_2/FiO_2) and with the history of use of sedation to achieve target RASS score were included in this study based on the electronic medical records. Patients were excluded if there was a history of cardiopulmonary arrest during admission, managed for burn wounds, or received a transfer from outside institutions. These exclusion criteria targeted patients with acute injury which could act as a confounding variable to the outcome of sedation.

Demographics, laboratory, type of sedative used, and individualized sedation plans of patients meeting the inclusion criteria were obtained through review of the patient's medical records. The incidence of complications

such as in-hospital mortality, sedation-related hypotension, and delirium were recorded. Data were transcribed onto the primary investigator's password-protected personal computer. Data was shared with the statistician through password-protected documents.

Sample Size

A minimum of 146 patients with ARDS are required using the formula for mean based on 90% power and a significance level of 5% based on the mean mechanical ventilation days of study by Tapaskar et al.[8]

Sampling Method

Consecutive sampling until the required sample size was met.

Statistical Analysis

Descriptive statistics were employed to summarize the general and clinical characteristics of the participants. To determine the differences in mean, median, and frequency between C-ARDS and non-C-ARDS groups, independent T-test, Mann-Whitney U test, and Fisher's Exact/Chi-square test were utilized, respectively. The odds ratio and the corresponding 95% confidence interval were calculated using binary logistic regression to determine the association between sedation practices with outcomes and complications. Missing variables were not replaced or estimated, and the null hypothesis was rejected at a 0.05 α-level of significance. All data analysis was conducted using R software version 4.2.2.

For this study, possible sources of bias include selection bias as patients were chosen from the intensive care units based on the diagnoses of acute respiratory distress syndrome which was unavoidable due to its retrospective design. Information bias was also a concern for this study; hence, missing variables were not replaced or estimated.

RESULTS

The medical records of 198 patients admitted to the ICU with ARDS during the study period were reviewed, and 48 patients were excluded for not meeting the inclusion criteria (Figure 1). Of the 150 patients meeting the inclusion criteria, 112 had C-ARDS, and 38 had non-C-ARDS.

Patient Characteristics

Detailed patient demographic and baseline characteristics are described in Table 1. Patients in the C-ARDS group had a median age of 61 years (41.07% females), and those in the non-C-ARDS had a median age of 54.5 years (42.11% females) with no intergroup differences. However, patients with C-ARDS had a significantly higher BMI (median 24.11, IQR 22.29-27.34) than those without C-ARDS (median 21.09, 20.59-22.18, p<0.001). Other comorbidities were considerably lower in C-ARDS patients than in non-C-ARDS patients (p=0.017). On admission, C-ARDS patients

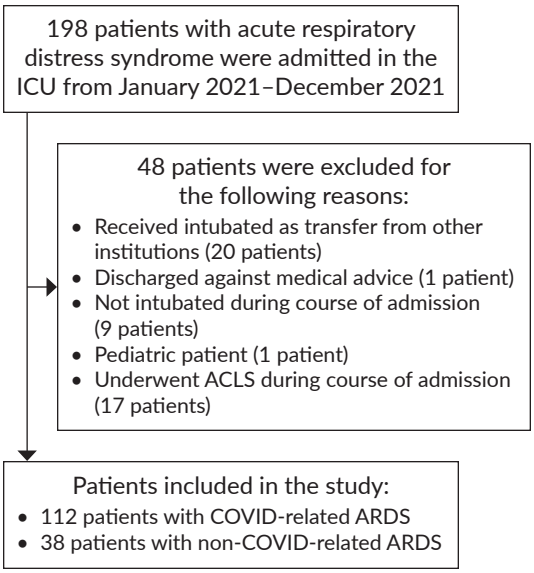

Figure 1. Flow diagram of patients who met the inclusion criteria.

had significantly lower oxygen saturation levels (median 85, IQR 66-93) than non-C-ARDS patients (median 96, IQR 91.25-98, p<0.001). Two patients had unappreciable oxygen saturation during admission.

The PaO_2/FiO_2 ratio differed significantly when sedation was decided between patients with or without C-ARDS (p<0.001). C-ARDS patients had a significantly higher maximum PEEP use than non-C-ARDS patients (p<0.001). The use of prone positioning was substantially more common in C-ARDS patients (40.18%) than in non-C-ARDS patients (2.63%, p<0.001). Assist/control+pressure control ventilation mode was used substantially less frequently in non-C-ARDS patients (31.58%) than in C-ARDS patients (52.68%, p=0.039).

Sedation Characteristics

Sedatives used, dosage, and duration of sedation in C-ARDS and non-C-ARDS patients are described in Table 2.

The distribution of RASS scores differed significantly between patients with C-ARDS and those without (p=0.038). A significantly higher proportion of patients in the C-ARDS group received benzodiazepine (midazolam) as well as non-benzodiazepine (fentanyl, dexmedetomidine, and propofol) sedatives than in non-C-ARDS groups (p<0.001). Diazepam was not used in either group. In addition, a significantly higher proportion of patients in the C-ARDS group (82.14% vs. 18.42) received more than one sedative (p<0.001). In terms of dosage of sedative, C-ARDS patients were prescribed significantly higher doses of midazolam (78 mg/d vs. 36 mg/d; p=0.01) and propofol (mean 2626±1312.97 mg/d vs. 1742±380.99 mg/d; p=0.007) although the dosage of fentanyl and dexmedetomidine did not differ between the two groups.

Table 1. Characteristics of Patients (n=150) with COVID-related Acute Respiratory Distress Syndrome (C-ARDS) and Non-COVID-related ARDS (Non-C-ARDS)

Variables	All (n=150)	C-ARDS (n=112)	Non-C-ARDS (n=38)	*p*
Age (years), Median (IQR)	60.50 (47.25-68.75)	61 (48-67)	54.50 (42-71)	0.733§
Sex, n (%)				
Male	88 (58.67)	66 (58.93)	22 (57.89)	>0.999†
Female	62 (41.33)	46 (41.07)	16 (42.11)	
BMI [n=64], *Median (IQR)*	23.31 (21.09-26.43)	24.11 (22.29-27.34)	21.09 (20.59-22.18)	**<0.001**§
Comorbidities, n (%)				
Hypertension	81 (54)	62 (55.36)	19 (50)	0.701†
Diabetes mellitus	50 (33.33)	40 (35.71)	10 (26.32)	0.388†
End-stage renal failure	19 (12.67)	14 (12.50)	5 (13.16)	>0.999†
Congestive heart failure	9 (6)	7 (6.25)	2 (5.26)	>0.999‡
Pulmonary disease	14 (9.33)	10 (8.93)	4 (10.53)	0.753‡
Liver disease	5 (3.33)	3 (2.68)	2 (5.26)	0.601‡
Others	53 (35.33)	33 (29.46)	20 (52.63)	**0.017**†
O_2 saturation during admission [n=148], Median (IQR)	89 (71.75-95.25)	85 (66-93)	96 (91.25-98)	**<0.001**§
Days to intubation since admission, Median (IQR)	1 (0-4)	0 (0-4)	1 (0-4.75)	0.306§
SOFA score on admission [n=149], Median (IQR)	5 (4-7)	5 (4-7)	6 (4-7)	0.507§
PaO_2/FiO_2 ratio when sedation decided [n=141], n (%)				
200-300	17 (12.06)	7 (6.31)	10 (33.33)	**<0.001**†
100-199	44 (31.21)	35 (31.53)	9 (30)	
<100	80 (56.74)	69 (62.16)	11 (36.67)	
Maximum PEEP used, Median (IQR)	15.50 (12-18)	16 (14-20)	10 (8-12)	**<0.001**§
Use of prone positioning, n (%)	46 (30.67)	45 (40.18)	1 (2.63)	**<0.001**‡
Ventilation mode used, n (%)				
Assist/control+Volume control	139 (92.67)	104 (92.86)	35 (92.11)	>0.999‡
Assist/control+Pressure control	71 (47.33)	59 (52.68)	12 (31.58)	**0.039**†
Assist/control+Volume control plus	35 (16.67)	22 (19.64)	3 (7.89)	0.130‡
Bilevel/Airway pressure release ventilation	20 (13.33)	17 (15.18)	3 (7.89)	0.407‡
Proportional assist ventilation	2 (1.33)	1 (0.89)	1 (2.63)	0.444‡

SOFA – Sequential organ failure assessment, PaO_2/FiO_2 – arterial oxygen partial pressure to fractional inspired oxygen ratio, PEEP – Positive end-expiratory pressure.

§Mann-Whitney U test, †Chi-square test, ‡Fisher's exact test

The distribution of number of days of midazolam, fentanyl, dexmedetomidine, and propofol use was also not statistically different between the two groups.

Clinical Outcomes

Interestingly, the median length of hospitalization (9 vs. 20 days; $p<0.001$) and duration of ventilator use (7 vs. 14.50 days; $p<0.001$) was over two times higher in patients without than those with C-ARDS (Table 3).

Nevertheless, a significantly higher proportion of patients in the C-ARDS group required treatment for hypotension (48.21% vs. 19.44%; $p=0.004$), which also had higher mortality (100% vs. 89.47%; $p=0.004$) than the non-C-ARDS group. No statistically significant between-group difference in the time to extubation and the occurrence of delirium was noted.

Our binary logistic regression analysis showed that the use of more than two sedatives [OR=24.26 (2.23-3310.35); $p=0.007$] and the simultaneous use of benzodiazepine and non-benzodiazepine sedatives [OR=31.09 (2.86-4240.37); $p=0.003$] was associated with mortality risk in the overall study population but when dichotomized into C-ARDS and non-C-ARDS groups was not statistically significant (Table 4).

In contrast, use of two sedatives [OR=0.25 (0.07-0.85); $p=0.032$], more than two sedatives [OR=0.28 (0.10-0.73); $p=0.009$] and the simultaneous use of benzodiazepine and non-benzodiazepine sedatives [OR=0.27 (0.10-0.68); $p=0.006$] was associated with lower odds of >14 days of ventilator use in the overall study population (Table 5).

The odds of >14 days of hospitalization was lower with single [OR=0.30 (0.09-0.93); $p=0.04$], dual [OR=0.28 (0.08-0.89); $p=0.036$], or multiple [OR=0.31 (0.11-0.78); $p=0.015$] sedative use, and with benzodiazepine [OR=0.18 (0.04-0.70); $p=0.017$] and simultaneous use of benzodiazepine/non-benzodiazepine [OR=0.30 (0.12-0.76); $p=0.012$] sedatives in the overall study population (Table 6).

Table 2. Sedation Characteristics and Sedative Use of Patients (n=150) with COVID-related Acute Respiratory Distress Syndrome (C-ARDS) and Non-COVID-related ARDS (Non-C-ARDS)

Variables	All (n=150)	C-ARDS (n=112)	Non-C-ARDS (n=38)	*p*
Richmond Agitation-Sedation Scale (RASS) Score Observed [n=124], n (%)				
0	16 (12.90)	10 (9.26)	6 (37.50)	**0.038**‡
-1	13 (10.48)	11 (10.19)	2 (12.50)	
-2	38 (30.65)	36 (33.33)	2 (12.50)	
-3	23 (18.55)	21 (19.44)	2 (12.50)	
-4	34 (27.42)	30 (27.78)	4 (25)	
Sedatives used, n (%)				
Midazolam [n=149]	113 (75.84)	101 (90.18)	12 (32.43)	**<0.001**†
Fentanyl [n=149]	88 (59.06)	78 (69.64)	10 (27.03)	**<0.001**†
Dexmedetomidine [n=149]	56 (37.58)	51 (45.54)	5 (13.51)	**0.001**†
Propofol [n=148]	85 (57.43)	81 (72.97)	4 (10.81)	**<0.001**‡
Number of sedatives used, n (%)				
None	24 (16)	4 (3.57)	20 (52.63)	**<0.001**†
Single	27 (18)	16 (14.29)	11 (28.95)	
Dual	25 (16.67)	22 (19.64)	3 (7.89)	
Multiple	74 (49.33)	70 (62.50)	4 (10.53)	
Sedation dose, Median (IQR)				
Midazolam (mg/day)	75.36 (49.56-120)	78 (50.50-122.50)	36 (25.50-66.67)	**0.010**§
Fentanyl (mcg/day)	1740 (1087-2418)	1825 (1094-2540)	1440 (926.70-1926.20)	0.127§
Dexmedetomidine (mcg/day)	778.70 (546-998.40)	810.70 (568-1001.70)	484 (402-590.70)	0.086§
Propofol (mg/day, mean)	2580 ± 1295.33	2626 ± 1312.97	1742 ± 380.99	**0.007***
Neuromuscular blockade use [n=52], n (%)	48 (92.31)	47 (94)	1 (50)	0.149‡
Duration of sedation (days), Median (IQR)				
Midazolam [n=114]				
1-7	74 (64.91)	67 (66.34)	7 (53.85)	0.469‡
8-14	30 (26.32)	26 (25.74)	4 (30.77)	
>14	10 (8.77)	8 (7.92)	2 (15.38)	
Fentanyl [n=84]				
1-7	55 (65.48)	47 (65.28)	8 (66.67)	>0.999‡
8-14	20 (23.81)	17 (23.61)	3 (25)	
>14	9 (10.71)	8 (11.11)	1 (8.33)	
Dexmedetomidine [n=57]				
1-7	43 (75.44)	39 (75)	4 (80)	>0.999‡
8-14	13 (22.81)	12 (23.08)	1 (20)	
>14	1 (1.75)	1 (1.92)	0	
Propofol [n=83]				
1-7	62 (74.70)	58 (73.42)	4 (100)	0.650‡
8-14	17 (20.48)	17 (21.52)	0	
>14	4 (4.82)	4 (5.06)	0	

§*Mann-Whitney U test*, **Independent t-test*, †*Chi-square test*, ‡*Fisher's exact test*

However, use of more than two sedatives and simultaneous use of benzodiazepine/non-benzodiazepine were associated with a higher risk of hypotension in the overall study population [OR=8.70 (2.94-32.35); p<0.001 and OR=6.31 (2.19-22.96); p=0.002] and the C-ARDS group [OR=15.11 (1.52-2032.89); p=0.017 and OR=11.51 (1.17-1541.91); p=0.034] but not the non-C-ARDS group (Table 7).

No statistically significant associations were observed between the number or type of sedatives used and the occurrence of delirium (Table 8).

DISCUSSION

This retrospective cohort study highlights the sedation practices and their impact on the clinical outcomes of patients with ADRS in the Philippine setting, covering the period of the initial roll-out of COVID-19 vaccination in the country and the Delta variant surge in 2021. Our findings indicate that patients with C-ARDS were more aggressively managed with multiple sedative use and higher sedation doses, and had shorter duration of hospitalization and ventilator use. The shorter duration of ventilator use was due to the high

Table 3. Adverse Outcomes in Patients (n=150) with COVID-related Acute Respiratory Distress Syndrome (C-ARDS) and Non-COVID-related ARDS (Non-C-ARDS)

Variables	All (n=150)	C-ARDS (n=112)	Non-C-ARDS (n=38)	*p*
Length of hospital stay (days), Median (IQR)	11.50 (7-20.75)	9 (6-17)	20 (12.50-28)	**<0.001**§
1-14, n (%)	93 (62)	80 (71.43)	13 (34.21)	**<0.001**†
>14, n (%)	57 (38)	32 (28.57)	25 (65.79)	
Duration of ventilation (days), Median (IQR)	9 (6-15)	7 (5-13)	14.50 (9.25-20.75)	**<0.001**§
1-14, n (%)	110 (73.33)	91 (81.25)	19 (50)	**<0.001**†
>14, n (%)	40 (26.67)	21 (18.75)	19 (50)	
Time to extubation (days) [n=5], Median (IQR)	3 (2-10)	3 (3-3)	6 (2-19)	>0.999§
1-7, n (%)	3 (60)	1 (100)	2 (50)	>0.999‡
8-14, n (%)	1 (20)	0	1 (25)	
>14, n (%)	1 (20)	0	1 (25)	
Complications, n (%)				
Hypotension requiring pressor [n=148]	61 (41.22)	54 (48.21)	7 (19.44)	**0.004**†
Delirium [n=148]	11 (7.43)	7 (6.25)	4 (11.11)	0.463‡
Mortality	146 (97.33)	112 (100)	34 (89.47)	**0.004**‡

§*Mann-Whitney U test*, †*Chi-square test*, ‡*Fisher's exact test*

Table 4. Association of Sedation Practices with Mortality in patients with COVID-related Acute Respiratory Distress Syndrome (C-ARDS) and Non-COVID-related ARDS (Non-C-ARDS)

Variables	Overall		C-ARDS		Non-C-ARDS	
	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*
Number of sedatives						
None	Reference	-	Reference	-	Reference	-
Single	8.95 (0.80-1228.85)	0.078	3.67 (0.02-726.41)	0.541	0.22 (0.002-2.56)	0.255
Dual	2.66 (0.40-29.03)	0.318	5 (0.03-986.68)	0.454	3 (0.22-31.45)	0.370
Multiple	24.26 (2.23-3310.35)	**0.007**	15.67 (0.08-3068.78)	0.229	0.56 (0.004-7.53)	0.698
Type of sedative						
None	Reference	-	Reference	-	Reference	-
Benzodiazepine only	5.70 (0.50-785.97)	0.180	2.78 (0.01-552.89)	0.628	0.45 (0.003-5.90)	0.592
Non-benzodiazepine only	1.47 (0.21-16.33)	0.707	1.67 (0.01-335.99)	0.807	1.15 (0.10-8.80)	0.895
Both	31.09 (2.86-4240.37)	**0.003**	19.89 (0.10-3892.94)	0.198	0.38 (0.003-4.85)	0.507

Table 5. Association of Sedation Practices with Ventilation Days >14 days in Patients with COVID-related Acute Respiratory Distress Syndrome (C-ARDS) and Non-COVID-related ARDS (Non-C-ARDS)

Variables	Overall		C-ARDS		Non-C-ARDS	
	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*
Number of sedatives						
None	Reference	-	Reference	-	Reference	-
Single	0.35 (0.10-1.11)	0.080	0.14 (0.01-1.71)	0.121	0.85 (0.20-3.53)	0.818
Dual	0.25 (0.07-0.85)	**0.032**	0.10 (0.01-1.18)	0.064	7 (0.57-986.68)	0.141
Multiple	0.28 (0.10-0.73)	**0.009**	0.27 (0.03-2.42)	0.212	0.43 (0.04-3.16)	0.413
Type of sedative						
None	Reference	-	Reference	-	Reference	-
Benzodiazepine only	0.31 (0.07-1.16)	0.093	0.09 (0.003-1.37)	0.097	1.50 (0.20-13.33)	0.690
Non-benzodiazepine only	0.40 (0.09-1.57)	0.202	0.17 (0.01-2.66)	0.224	0.75 (0.12-4.28)	0.745
Both	0.27 (0.10-0.68)	**0.006**	0.24 (0.03-2.08)	0.163	1 (0.15-6.60)	>0.999

Table 6. Association of Sedation Practices with Hospital Stay >14 days in Patients with COVID-related Acute Respiratory Distress Syndrome (C-ARDS) and Non-COVID-related ARDS (Non C-ARDS)

Variables	Overall		C-ARDS		Non-C-ARDS	
	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*
Number of sedatives						
None	Reference	-	Reference	-	Reference	-
Single	0.30 (0.09-0.93)	**0.040**	0.14 (0.01-1.71)	0.121	0.93 (0.21-4.23)	0.918
Dual	0.28 (0.08-0.89)	**0.036**	0.29 (0.03-2.95)	0.275	3.89 (0.31-550.19)	0.328
Multiple	0.31 (0.11-0.78)	**0.015**	0.49 (0.06-4.29)	0.489	0.56 (0.07-4.30)	0.559
Type of sedative						
None	Reference	-	Reference	-	Reference	-
Benzodiazepine only	0.18 (0.04-0.70)	**0.017**	0.09 (0.003-1.37)	0.097	0.81 (0.11-7.25)	0.835
Non-benzodiazepine only	0.45 (0.11-1.70)	0.244	0.17 (0.01-2.66)	0.224	1.35 (0.22-11.13)	0.757
Both	0.30 (0.12-0.76)	**0.012**	0.46 (0.05-3.98)	0.448	1.08 (0.16-9.20)	0.940

Table 7. Association of Sedation Practices with Hypotension in Patients with COVID-related Acute Respiratory Distress Syndrome (C-ARDS) and Non-COVID-related ARDS (Non-C-ARDS)

Variables	Overall		C-ARDS		Non-C-ARDS	
	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*
Number of sedatives						
None	Reference	-	Reference	-	Reference	-
Single	1.14 (0.26-5.16)	0.863	2.33 (0.17-377.06)	0.569	0.89 (0.11-5.56)	0.903
Dual	1.94 (0.50-8.47)	0.346	4.35 (0.38-605.76)	0.272	9.40e-08 (NA-8.56e+120)	0.994
Multiple	8.70 (2.94-32.35)	**<0.001**	15.11 (1.52-2032.89)	**0.017**	12 (1.19-283.34)	0.053
Type of sedative						
None	Reference	-	Reference	-	Reference	-
Benzodiazepine only	1.07 (0.19-5.61)	0.935	3.32 (0.24-482.80)	0.412	3.46e-08 (NA-1.63e+97)	0.995
Non-benzodiazepine only	1.36 (0.23-7.32)	0.716	2.08 (0.09-332.34)	0.663	1.60 (0.18-11.21)	0.640
Both	6.31 (2.19-22.96)	**0.002**	11.51 (1.17-1541.91)	**0.034**	4 (0.56-30.53)	0.161

Table 8. Association of Sedation Practices with Delirium in Patients with COVID-related Acute Respiratory Distress Syndrome (C-ARDS) and Non-COVID-related ARDS (Non-C-ARDS)

Variables	Overall		C-ARDS		Non-C-ARDS	
	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*	Crude Odds Ratio (95% CI)	*p*
Number of sedatives						
None	Reference	-	Reference	-	Reference	-
Single	2.50 (0.48-18.78)	0.303	0.87 (0.04-136.21)	0.937	5.14 (0.82-43.74)	0.093
Dual	1.50 (0.23-12.24)	0.673	1.62 (0.12-232)	0.754	7.78e-08 (NA-2.22e+260)	0.997
Multiple	0.46 (0.07-3.70)	0.417	0.47 (0.04-66.41)	0.658	7.78e-08 (NA-4.93e+132)	0.996
Type of sedative						
None	Reference	-	Reference	-	Reference	-
Benzodiazepine only	1.47 (0.16-13.35)	0.716	1.17 (0.05-184.63)	0.925	2.25 (0.09-30.14)	0.546
Non-benzodiazepine only	4.40 (0.73-35.75)	0.117	2.08 (0.09-332.34)	0.663	6.75 (0.86-66.80)	0.074
Both	0.61 (0.12-4.46)	0.571	0.59 (0.05-81.34)	0.746	7.78e-08 (NA-1.39e+179)	0.995

mortality of these patients after a relatively shorter hospital stay compared to the non-C-ARDS group. The C-ARDS group had a 100% mortality, which may be attributed to the unvaccinated population and the high rates of nosocomial infections at the time, potentially impacting the findings on the duration of hospitalization and ventilator use. ARDS by itself has an overall hospital death rate of 40 percent, with commensurate increases based on severity.[14-16]

Nonetheless, a relatively higher proportion of C-ARDS experienced adverse events, specifically hypotension, than patients in the non-C-ARDS group. Although multiple sedative use and cotreatment with benzodiazepine and non-benzodiazepine sedatives were associated with a higher risk of hypotension and mortality, they were associated with lower odds of prolonged use of ventilator or duration of hospitalization in the overall study cohort. When dichotomized by COVID-19 status, multiple sedative use and cotreatment with benzodiazepine and non-benzodiazepine sedatives were associated with a higher risk of hypotension in the C-ARDS but not the non-C-ARDS group. In fact, none of the studied clinical outcomes were associated with the number or type of sedative in the non-C-ARDS group. Hence, C-ARDS patients with these sedation practices must be carefully monitored to address this complication adequately.

Thus, our study provides evidence that aggressive utilization of sedatives poses an additional risk of hypotension in C-ARDS compared to non-C-ARDS patients. The relevance of this finding becomes particularly important given the ARDS severity and pre-existing comorbidities of patients with COVID-19. For instance, C-ARDS patients in our cohort had lower O_2 saturation, with about two-thirds exhibiting a PaO_2/FiO_2 ratio of <100 and thus requiring higher PEEP. The initiation of sedation based on the PaO_2/FiO_2 ratio corresponds with the level of ARDS severity[17,18]; those with severe C-ARDS were more likely to be sedated. The increased use of sedation in C-ARDS patients has been previously linked to high respiratory drive and intense inflammatory responses.[8,11,13] The increased use of sedatives has also been linked to the practice of lung recruitment maneuvers such as high PEEP and prone positioning, both of which were significantly employed in our C-ARDS study group. Prone positioning has been used in ARDS patients to reduce lung compression and enhance perfusion.[19] However, based on a recent meta-analysis, there is insufficient evidence to support the efficacy of proning in COVID-19 intubated patients in terms of survival.[20]

Sedation characteristics such as depth of sedation, choice of sedative, number of sedatives, and sedation doses significantly differed between the two groups. C-ARDS patients showed deeper levels of sedation, received a median number of four sedatives, and had higher doses of midazolam and propofol compared to the non-C-ARDS group. The difference in RASS scores may be due to the high respiratory drive and the use of lung recruitment maneuvers to achieve ventilatory synchrony. This contrasts a study that showed no significant difference in the median RASS scores of COVID-19 and non-C-ARDS patients.[8] Although a 2021 guideline recommended the use of propofol and dexmedetomidine for mechanically ventilated patients not undergoing cardiac surgery,[21] it is prudent to mention that the choice of sedatives in this study was occasionally directed by availability due to drug shortages. Hence, achieving goal RASS was done through the use of any available benzodiazepines or non-benzodiazepine agents.

Further, C-ARDS patients in our cohort had significantly higher BMIs and were mostly overweight based on Asian BMI (23-27.99 kg/m^2). This was comparable to the Philippine CORONA study in which the median BMI was 25 kg/m^2, and overweight patients accounted for 32.8% of the study group.[22] The higher proportion of overweight adults with C-ARDS was also noted in the PRoVENT-COVID study, in which 48.3% of their study population was overweight.[23] The mechanisms by which increasing BMI may lead to risk of critical COVID-19 infection include the adipose tissue acting as a possible reservoir for viral production, impairment in immune function, and increased inflammatory response.[24-26]

Interestingly, we did not find delirium as a significant complication of sedation use in either C-ARDS or non-C-ARDS groups. Previous studies have inconsistently reported the risk of delirium with sedation in patients with COVID-19. For instance, studies by Rasulo et al.[27] and Pun et al.[28] showed a higher risk of delirium with sedation in patients with C-ARDS compared to non-C-ARDS groups. In contrast, Flinspach et al.[11] did not observe protracted delirium in C-ARDS patients. In the current study, the lack of significant delirium despite high sedation use is likely due to the lack of standard ICU protocol of sedation holidays and delirium checks in the hospital among sedated patients.

The result of this study reflects the need for a hospital-wide sedation protocol. This would include the preparation of a sedation algorithm that would direct medical staff in different settings whether the emergency room, wards, or intensive care units regarding the initial sedative choice and sedation dose for the critically ill patients. This would also reflect the need for education of hospital staff regarding the side effects of these sedatives and a protocol regarding sedation holidays and delirium checks for these patients.

Limitations

The study has several limitations that may limit the generalizability of our findings. First, this is a retrospective cohort study, and our analysis was limited by the data available in the medical records. Second, this study only included admitted patients in the intensive care unit and did not include patients in the ward settings. Third, three-fourths of our study population had COVID-19, as the Philippine General Hospital was designated as the national COVID-19 referral center in the early phase of the pandemic in March 2020, receiving around 9,300 admissions from across the region. Fourth, as this was a retrospective study with high

mortality in the C-ARDS group as well as lack of propensity score matching between the two groups, sensitivity analysis was not pursued in this study. This could be a further explored in future studies with a prospective approach to control for confounders.

CONCLUSION

This study demonstrates that among C-ARDS patients, there is higher sedative use, both in number and dosage, compared to non-C-ARDS. The use of multiple sedatives and combination use of benzodiazepines and non-benzodiazepine agents in C-ARDS are significantly associated with hypotension requiring pressor. However, given the limitations of our study, prospective studies with a balanced proportion of C-ARDS and non-C-ARDS patients, and inclusive of patients on non-invasive ventilation but requiring sedation, focusing will be necessary to direct future sedation practices and possible implementation of a hospital-wide sedation protocol.

Statement of Authorship

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Author Disclosure

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