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Risk Factors and Outcomes Associated With Re-Intubation Secondary to Respiratory Failure in Patients With COVID-19 ARDS

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BACKGROUND: COVID-19 is associated with variable symptoms and clinical sequelae. Studies have examined the clinical course of these patients, finding a prolonged need for invasive ventilation and variable re-intubation rates. However, no research has investigated factors and outcomes related to re-intubation secondary to respiratory failure among patients with COVID-19 with ARDS. METHODS: We conducted a single-center, retrospective study on subjects intubated for ARDS secondary to COVID-19. The primary outcome was re-intubation status; secondary outcomes were hospital and ICU stay and mortality. Data were analyzed using between-group comparisons using chi-square testing for categorical information and Student *t* test for quantitative data. Univariate and multivariate logistic regression was performed to determine factors related to re-intubation and mortality as dependent variables. RESULTS: One hundred and fourteen subjects were included, of which 32% required re-intubation. No between-group differences were detected for most demographic variables or comorbidities. No differences were detected in COVID-19 treatments, noninvasive respiratory support, mechanical circulatory support, or duration of ventilation. Midazolam (odds ratio [OR] 5.55 [95% CI 1.83–16.80], *P* = .002), fentanyl (OR 3.64 [95% CI 1.26–10.52], *P* = .02), and APACHE II scores (OR 1.08 [95% CI 1.030–1.147], *P* = .005) were independently associated with re-intubation (area under the curve = 0.81). Re-intubated subjects had extended hospital (36.7 ± 22.7 d vs 26.1 ± 12.1 d, *P* = .01) and ICU (29.6 ± 22.4 d vs 15.8 ± 10.4 d, *P* < .001) stays. More subjects died who failed extubation (49% vs 3%, *P* < .001). Age (OR 1.07 [95% CI 1.02–1.23], *P* = .005), male sex (OR 4.9 [95% CI 1.08–22.35], *P* = .041), positive Confusion Assessment Method for the ICU (CAM-ICU) (OR 5.43 [95% CI 1.58–18.62], *P* = .007), and re-intubation (OR 12.75 [95% CI 2.80–57.10], *P* < .001) were independently associated with death (area under the curve = 0.93). CONCLUSIONS: Midazolam, fentanyl, and higher APACHE II scores were independently associated with re-intubation secondary to respiratory failure in subjects with COVID-19–related ARDS. Furthermore, age, male sex, positive CAM-ICU, and re-intubation were independently associated with mortality. Re-intubation also correlated with prolonged hospital and ICU stay.
Key words: COVID-19; ARDS; extubation failure; respiratory failure; mechanical ventilation; re-intubation; mortality; delirium; sedation; analgesic. [Respir Care 0;0(0):1–●. © 2023 Daedalus Enterprises]

Introduction

Infection with SARS-CoV-2 is associated with variable symptoms and clinical sequelae. Patients who progress to ARDS often have poor outcomes.[1] Approximately 12–24% of hospitalized and 65–80% of critically ill patients with COVID-19 required invasive mechanical ventilation during the early waves of the pandemic, with mortality rates as high as 76%.[2-5] In general ICU populations, extubation failure occurs in 10–20% of invasively ventilated patients and is associated with mortality rates ranging from 25–50%.[6] Several observational studies found re-intubation rates between 12–33% in subjects with COVID-19, although time frames and etiologies of failure varied in this research.[7-12]

Few studies have investigated specific predictive factors associated with re-intubation in subjects with COVID-19.[7,8,11,12] Certain groups were at greater risk of adverse events from the virus, with potential variations depending on demographic factors, patient acuity, and indications for mechanical ventilation. As a large, urban, tertiary-care academic facility, our hospital treated a racially and ethnically diverse population with COVID-19. In addition, we received patients transferred

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from other institutions for higher levels of care. Our study sought to ascertain the re-intubation rate at our facility and determine the comorbidities, clinical factors, and outcomes associated with extubation failure secondary to respiratory failure in a diverse cohort of invasively ventilated subjects with COVID-19–related ARDS.

Methods

Subjects

We conducted a single-center, retrospective study on subjects intubated for ARDS secondary to COVID-19 from March 2020–February 2022. All patients placed on invasive mechanical ventilation with laboratory-confirmed COVID-19 were screened for study inclusion. Subjects were included if they met Berlin criteria for ARDS[13] upon intubation, were ventilated ≥ 24 h, passed a spontaneous breathing trial (SBT), and were electively extubated. Patients were excluded for the following reasons: intubated or re-intubated for indications other than acute respiratory failure, including incidental COVID-19 infection and upper-airway obstruction; re-intubated > 7 d post initial extubation; received tracheostomy before any planned extubation; expired on the ventilator before planned extubation; unplanned extubation; do not resuscitate/do not intubate postextubation; or transferred to an outside hospital on a ventilator without a planned extubation attempt. A total of 114 subjects were enrolled. Subjects were grouped according to re-intubation status within 7 d following the first planned extubation.

QUICK LOOK

Current knowledge

Several associated risk factors and outcomes related to extubation failure among patients with COVID-19 have been identified. Specific ventilator characteristics, inflammatory markers, hemodialysis, pressor requirements, neurological status, old age, body mass index, and S_{pO_2}/F_{IO_2} and P_{aO_2}/F_{IO_2} have been identified to correlate with the risk of re-intubation. Failed extubation results in worse morbidity and increased mortality.

What this paper contributes to our knowledge

Use of midazolam and fentanyl within 48 h prior to extubation and higher APACHE II scores at ICU admission were associated with a higher risk for re-intubation secondary to respiratory failure within one week of planned extubation. In addition, positive Confusion Assessment Method for the ICU and re-intubation status correlated with higher mortality, with re-intubation also associated with extended hospital and ICU lengths of stay.

Clinical Protocols

Respiratory support. For subjects with COVID-19, respiratory therapists delivered noninvasive respiratory support, including conventional oxygen therapy (nasal cannula, oxygen mask, non–rebreathing mask [NRB]), high-flow nasal cannula (HFNC), or noninvasive ventilation (NIV), based on approved hospital-wide protocols and guidance for patients with COVID-19 with acute respiratory failure. Support was generally escalated depending on the degree of hypoxemia and work of breathing (WOB) as evaluated by accessory muscle use and breathing frequency (f). Subjects with moderate hypoxemia (S_{pO_2} 90–92% and f < 28 breaths/min) were placed on an NRB, often with dual use of a nasal cannula to maximize F_{IO_2} and reduce entrainment of room air. Subjects with moderate-to-severe hypoxemia (S_{pO_2} < 90% on 100% NRB at flows of 10–15 L/min) were placed on HFNC. NIV was used as a therapeutic challenge during initial resuscitation in dyspneic and hypoxemic subjects with COVID-19 or when low levels of support were needed in subjects with stable WOB. Staff also encouraged awake prone positioning as tolerated in spontaneously breathing subjects.

During the initial patient surge, controlled intubation was favored. In contrast, more prolonged trials of noninvasive respiratory support were used as the pandemic progressed as recommended by the COVID-19 Treatment Guidelines Panel (https://www.covid19treatmentguidelines.nih.gov. *Accessed January 11, 2023*).[14] In addition, providers intubated subjects immediately for acute changes in mental status, rapidly worsening respiratory distress, hemodynamic instability, acute

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kidney injury, or other contraindications for noninvasive respiratory support. Subjects who failed maximal HFNC or NIV therapy, based on S_{pO_2} (< 88%) and WOB (f > 40 breaths/min, accessory muscle use), were also intubated.

According to guidance created early in the pandemic, clinicians provided invasive mechanical ventilation according to MedStar's Emergency Medicine and Critical Care Advisory Group. Initial ventilator settings included tidal volumes (V_T) of 8 mL/kg/ideal body weight, PEEP 8–10 cm H_2O, and F_{IO_2} weaned to 0.60 as soon as possible. The advisory group recommended the ARDS Network protocol for COVID-19–induced severe respiratory failure with V_T of 4–6 mL/kg/ideal body weight and PEEP titration to maintain plateau pressure < 30 cm H_2O and driving pressure < 14 cm H_2O. Pronation for at least 16 h per day and inhaled pulmonary vasodilators were used in subjects with a P_{aO_2}/F_{IO_2} < 150 mm Hg and those requiring F_{IO_2} > 0.60. Subjects were supinated when the following criteria were consistently met: plateau pressure < 25 cm H_2O, F_{IO_2} < 0.50, and $P_{aO_2}/F_{IO_2} \geq 300$ mm Hg.

Medications. Intubated subjects were sedated to a Richmond Agitation-Sedation Scale (RASS) score of 0 to −2 based on ventilator synchrony. However, a RASS score of −4 was targeted when neuromuscular blocking agents (NMBAs) were used or if the subject was pronated. Propofol and dexmedetomidine were recommended as first-line sedative agents,[15] with ketamine and benzodiazepines used as second-line treatments in subjects with seizures, contraindications to propofol, or those refractory to the combination of propofol and dexmedetomidine. Dexmedetomidine was used as adjuvant therapy when clinicians could not maintain a RASS between 0 to −2 on propofol or when propofol inhibited progress toward extubation. Dexmedetomidine was also added in subjects with documented intolerances to other sedative agents or those experiencing adverse effects. Ketamine with a lidocaine adjuvant was recommended if agitation was still not controlled, with consideration for lorazepam, clonazepam, or atypical antipsychotics as needed for rescue therapy. Phenobarbital was used for sedation in uncontrolled, refractory agitation. Recommendations for first-line pain management included hydromorphone or fentanyl infusions with as-needed boluses.[15] Ketamine, lidocaine, or remifentanil were used for refractory pain management.[15] Paralysis was achieved as needed with vecuronium or rocuronium intravenous boluses provided every 2 h for ventilator asynchrony and cisatracurium or vecuronium infusions as second-line agents. Nursing staff obtained Confusion Assessment Method for the ICU (CAM-ICU) scores once per shift.

Anticoagulation with enoxaparin or unfractionated heparin was provided based on evolving published guidelines recommended by the COVID-19 Treatment Guidelines Panel, subject presentation, and creatinine clearance. Therapeutic anticoagulation was provided for subjects at high risk with suspected or confirmed thromboembolism, whereas prophylactic treatment was given to subjects at average and moderate clotting risk. In addition, remdesivir, tocilizumab, dexamethasone, and convalescent plasma were delivered based on the COVID-19 Treatment Guidelines Panel.

Tracheostomy. Given the unclear evidence guiding tracheostomy timing in patients with COVID-19, theoretical considerations were used to determine the need for this procedure, including the potential for viral spread, subject stability, and radiographic findings. Tracheostomy was considered in subjects > 7 d post diagnosis, who showed no clinical or radiological signs of remission within 10 d of intubation, with F_{IO_2} < 0.60, PEEP < 8 cm H_2O, f < 30 breaths/min, S_{pO_2} > 92%, and hemodynamic stability.

Extubation. According to the MedStar Washington Hospital Center Clinical Guide for Extubation, subjects who showed improvement in their underlying respiratory failure with P_{aO_2} > 60 mm Hg; S_{pO_2} of 88–92%; $F_{IO_2} \leq 0.4$; PEEP ≤ 5 cm H_2O; acceptable pH and CO_2; plateau pressure < 30; absence of auto PEEP; and were hemodynamically stable, able to follow commands, and initiate inspiratory effort underwent an SBT. SBTs were performed with pressure support ventilation of 5 cm H_2O and PEEP of 5 cm H_2O for a minimum of 30 min. Subjects were considered to have failed the SBT if they became altered with Glasgow coma scale < 8, agitated, hemodynamically unstable with heart rate > 130 or < 50 beats/min, systolic blood pressure > 180 mm Hg or < 90 mm Hg, f > 35 breaths/min or < 10 breaths/min, S_{pO_2} < 88% with F_{IO_2} > 0.60, or a rapid shallow breathing index (RSBI) of > 105. If subjects could tolerate the SBT while remaining hemodynamically stable and had an RSBI < 105, cuff leak, and minimal endotracheal tube (ETT) secretions, they were extubated.

Data Analysis

After obtaining institutional review board approval from MedStar Research Health Institute (STUDY00003370), we collected demographic, clinical, and outcome information for 114 subjects from the electronic medical record using a standardized format. Demographic data included age, sex, and race. Clinical information included body mass index (BMI), comorbid conditions, the Acute Physiology and Chronic Health Evaluation (APACHE II) scores at ICU admission, time to and duration of invasive mechanical ventilation, sedative and pain medications within 48 h before the planned extubation, CAM-ICU scores within 48 h before the planned extubation and 7 d postextubation, COVID-19 therapeutics (eg, remdesivir, tocilizumab, and dexamethasone) provided during hospitalization, and postextubation respiratory support. The primary outcome variable was re-intubation secondary to respiratory failure. Respiratory failure was defined as S_{pO_2} < 88% and increased WOB

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(f > 40 breaths/min or accessory muscle use with or without the use of HFNC or NIV) within one week of extubation. The secondary outcome variables were hospital and ICU length of stay (LOS) and mortality.

Categorical values are presented as numbers (%), whereas continuous data are presented as either mean ± SD or median (range), depending on skew. Between-group comparisons were made using chi-square testing for categorical information and Student *t* test for quantitative data with log transformation when appropriate, following normality testing using Shapiro-Wilk. Univariate logistic regression was performed to determine factors related to re-intubation and mortality as separate dependent variables. All independent variables with a $P \leq .10$ were examined in multivariate logistic regression models to assess independent associations with the outcomes of interest. The regression model obtained sensitivity, specificity, and optimum cut-points for significant continuous variables. Data were imported into SAS 9.4 (SAS Institute, Cary, North Carolina) from Excel (Microsoft, Redmond, Washington) and analyzed with a *P* value < .05 delineated as statistically significant.

Results

Re-Intubation

There were 114 subjects included in the study cohort, including 77 who remained extubated after planned extubation and 37 who required re-intubation secondary to respiratory failure within 7 d, for a rate of 32%. There were no differences in sex ($P = .30$), race ($P = .65$), BMI ($P = .28$), and dominant variant by time frame (alpha, beta, delta, omicron, $P = .22$) as documented by the United States Centers for Disease Control and Prevention (https://www.cdc.gov/mmwr/volumes/70/wr/mm7003e2.htm. *Accessed March 22, 2023*) between subjects requiring re-intubation and those who did not. There were also no differences in several significant comorbidities, including diabetes mellitus ($P = .051$), pulmonary disease ($P = .93$), cardiac disease ($P = .96$), or chronic kidney disease ($P = .10$). However, subjects who were re-intubated were more likely to be older (60.4 ± 14.8 y vs 54.2 ± 14.4 *y*, $P = .03$), have hypertension (27 [73%] vs 41 [53%], $P = .042$), and have higher APACHE II scores at ICU admission (23.3 ± 9.1 vs 18.8 ± 9.6, $P = .02$) and positive CAM-ICU scores within 48 h before the planned extubation and 7 d postextubation (22 [58%] vs 27 [36%], $P = .03$) than those who remained extubated (Table 1).

There were no statistically significant differences between those who required re-intubation and those who did not concerning the use of COVID-19 therapeutics, including remdesivir ($P = .48$), dexamethasone ($P = .35$), and tocilizumab ($P = .22$). However, there were significantly more subjects who required propofol ($P = .003$), midazolam ($P < .001$), and fentanyl ($P < .001$) use within 48 h prior to extubation in the re-intubated group. There were no between-group differences in ketamine use ($P = .33$) (Table 2). Supportive therapy, including the use of NMBA ($P = .89$), pronation ($P = .55$), inhaled pulmonary vasodilators ($P = .99$), and extracorporeal membrane oxygenation ($P = .17$), in addition to postextubation respiratory support ($P = .49$) (Table 3) was similar between groups. Time from admission to first intubation was not significantly different between groups (4.75 ± 6.78 d vs 2.35 ± 3.11 d, $P = .25$), including when separated by sex (5.33 ± 6.22 d vs 2.31 ± 2.83 d, $P = .33$ for males and 3.81 ± 7.77 d vs 2.39 ± 3.42 d, $P = .42$ for females) (Table 4).

Table 1. Demographics

Variable ($N = 114$)	Re-Intubated ($n = 37$)	Not Re-Intubated ($n = 77$)	*P*
Age, y	60.40 (± 14.80)	54.20 (± 14.40)	.03
Male/female (male %)	23/14 (62)	40/37 (52)	.30
BMI, kg/m^2	32.60 (± 8.90)	34.60 (± 9.60)	.28
Race			.65
Black	23 (62)	42 (55)	
White	4 (11)	6 (8)	
Hispanic	8 (22)	24 (31)	
Asian	0	2 (3)	
Other	2 (5)	3 (4)	
Dominant COVID-19 variants			.22
Alpha	22 (59)	53 (69)	
β	10 (27)	16 (21)	
Δ	2 (5)	5 (6)	
Omicron	4 (10)	2 (3)	
Comorbidities			
Diabetes mellitus	21 (57)	29 (38)	.051
Hypertension	27 (73)	41 (53)	.042
Pulmonary disease	6 (16)	13 (17)	.93
Chronic kidney disease	10 (27)	11 (14)	.10
Scores			
APACHE II score	23.30 (± 9.10)	18.80 (± 9.60)	0.02
Positive CAM-ICU	22 (58)	27 (36)	0.03

Data are presented as *n* (%) or mean (± SD).
BMI = body mass index
APACHE II = Acute Physiology and Chronic Health Evaluation II
CAM-ICU = Confusion Assessment Method for the ICU

Re-intubated subjects had a similar initial duration of ventilation as those who were not re-intubated (10.7 ± 6.7 d vs 10.3 ± 6.7 d, $P = .74$) but had extended hospital (36.7 ± 22.7 d vs 26.1 ± 12.1 d, $P = .01$) and ICU (29.6 ± 22.4 d vs 15.8 ± 10.4 d, $P < .001$) LOSs. Furthermore, significantly more subjects who failed extubation died (49% vs 3%, $P < .001$) (Table 4).

The APACHE II scores at ICU admission (odds ratio [OR] 1.08 [95% CI 1.03–1.13], $P < .001$); postextubation respiratory support (OR 1.91 [95% CI 1.05–3.49], $P = .034$); history of hypertension (OR 2.18 [95% CI 0.94–5.06], $P = .067$); pulmonary (OR 0.23 [95% CI 0.06–0.86],

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Table 2. Major COVID-19 Therapeutics and Sedatives

Variable ($N = 114$)	Re-Intubated ($n = 37$)	Not Re-Intubated ($n = 77$)	P
Remdesivir	15 (41)	26 (34)	.48
Dexamethasone	25 (68)	45 (58)	.35
Tocilizumab	5 (14)	18 (23)	.22
Propofol	15 (41)	12 (16)	.003
Midazolam	21 (57)	11 (14)	< .001
Fentanyl	31 (84)	38 (49)	< .001
Ketamine	5 (14)	6 (8)	.33

Data are presented as *n* (%).

Table 3. Supportive Therapy

Variable ($N = 114$)	Re-Intubated ($n = 37$)	Not Re-Intubated ($n = 77$)	P
NMBA	11 (30)	22 (29)	.89
Prone position	19 (51)	35 (45)	.55
Inhaled pulmonary vasodilator	12 (32)	25 (32)	.99
ECMO	6 (16)	6 (8)	.17
Postextubation respiratory support			.49
Conventional O_2	13 (35)	36 (47)	
HFNC	14 (38)	23 (30)	
NIV	10 (27)	18 (23)	

Data are presented as *n* (%).
NMBA = neuromuscular blocking agent
ECMO = extracorporeal membrane oxygenation
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation

$P = .03$) and chronic kidney disease (OR 3.09 [95% CI 1.16–8.24], $P = .02$); and propofol (OR 4.44 [95% CI 1.77–11.15], $P = .002$), midazolam (OR 8.71 [95% 3.39–22.30], $P < .001$), fentanyl (OR 5.34 [95% CI 2.17–13.30], $P < .001$), and ketamine use (OR 4.75 [95% CI 1.19–19.03], $P = .03$) were significant in the univariate analysis and thus entered as independent variables into a backward, stepwise, multiple logistic regression analysis with re-intubation as the dependent variable (Table 5). Results showed APACHE II score (OR 1.08 [95% CI 1.03–1.15, $P = .005$), midazolam (OR 5.55 [95% CI 1.83–16.8], $P = .002$), and fentanyl use (OR 3.64 [95% CI 1.26–10.52, $P = .02$) were independently associated with re-intubation (model area under the curve = 0.81). See Figure 1 for receiver operating characteristic (ROC) curve results.

Morbidity and Mortality

Significant univariate results with mortality as the dependent variable included age (OR 1.05 [95% CI 1.01–1.09], $P = .009$); male sex (OR 3.99 [95% CI 1.24–12.85], $P = .02$); positive CAM-ICU score (OR 4.37 [95% CI 1.68–11.34], $P = .002$); dominant variant by time frame (OR 1.55 [95% CI 0.93–2.58], $P = .09$); re-intubation status (OR 29.30 [95% CI 3.60–23.55], $P = .002$); comorbid diabetes (OR 2.86 [95% CI 1.04–7.83], $P = .042$); and dexamethasone (OR 2.96 [95% CI 0.92–9.54], $P = .068$), tocilizumab (OR 0.17 [95% CI 0.02–1.36, $P = .10$]), fentanyl (OR 3.09 [95% CI 0.96–9.95], $P = .058$), and ketamine use (OR 3.10 [95% CI 0.81–11.85], $P = .10$) (Table 6). In the final model, age (OR 1.07 [95% CI 1.02–1.23], $P = .005$), male sex (OR 4.90 [95% CI 1.08–22.35], $P = .041$), positive CAM-ICU scores (OR 5.43 [95% CI 1.58–18.62], $P = .007$), and re-intubation (OR 12.75 [95% CI 2.80–57.10], $P < .001$) were independently associated with death (model area under the curve = 0.93). See Figure 2 for ROC curve results.

Discussion

Re-intubation

Various COVID-19 research has examined complications and morbidities associated with this novel illness. Our study focused on predominantly minority subjects infected with

Table 4. Intubation Time, Length of Stay, and Mortality

Variable ($N = 114$)	Re-Intubated ($n = 37$)	Not Re-Intubated ($n = 77$)	P
Intubation time and duration of initial mechanical ventilation			
Time from admission to first intubation, d	4.75 (± 6.78)	2.35 (± 3.11)	.25
Time from admission to first intubation (males), d	5.33 (± 6.22)	2.31 (± 2.83)	.33
Time from admission to first intubation (females), d	3.81 (± 7.77)	2.39 (± 3.42)	.42
Duration of initial invasive mechanical ventilation, d	10.70 (± 6.70)	10.30 (± 6.70)	.74
Secondary outcomes			
Hospital LOS, d	36.70 (± 22.70)	26.10 (± 12.10)	.01
ICU LOS, d	29.60 (± 22.40)	15.80 (± 10.40)	< .001
Mortality	18 (49)	2 (3)	< .001

Data are presented as mean (± SD) or *n* (%).
LOS = length of stay

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Table 5. Univariate Analysis for Re-Intubation

Variable	OR	CI	*P*
Age	1.01	0.98–1.04	.28
Male	1.37	0.64–2.94	.41
BMI	0.97	0.94–1.02	.23
Race	1.09	0.83–1.41	.53
APACHE II score	1.08	1.03–1.13	< .001
Positive CAM-ICU score	1.58	0.80–3.13	.19
Dominant variant by time frame	1.34	0.85–2.09	.20
Diabetes mellitus	1.89	0.88–4.04	.10
Hypertension	2.18	0.94–5.06	.067
Pulmonary disease	0.23	0.06–0.86	.03
Cardiac Disease	1.27	0.52–3.12	.60
Chronic kidney disease	3.09	1.16–8.24	.02
Remdesivir	1.13	0.52–2.48	.74
Dexamethasone	1.70	0.77–3.75	.19
Tocilizimab	0.98	0.38–2.50	.97
Propofol	4.44	1.77–11.15	.002
Midazolam	8.71	3.39–22.30	< .001
Fentanyl	5.34	2.17–13.30	< .001
Ketamine	4.75	1.19–19.03	.03
Time from admission to first intubation	1.10	0.92–1.32	.27
Duration of initial mechanical ventilation	0.99	0.94–1.05	.73
Postextubation respiratory support	1.91	1.05–3.49	.034
Significant multivariate analysis for re-intubation			
APACHE II score	1.08	1.03–1.15	.005
Midazolam	5.55	1.83–16.80	.002
Fentanyl	3.64	1.26–10.52	.02

OR = odds ratio
BMI = body mass index
APACHE II = Acute Physiology and Chronic Health Evaluation II
CAM-ICU = Confusion Assessment Method for the ICU

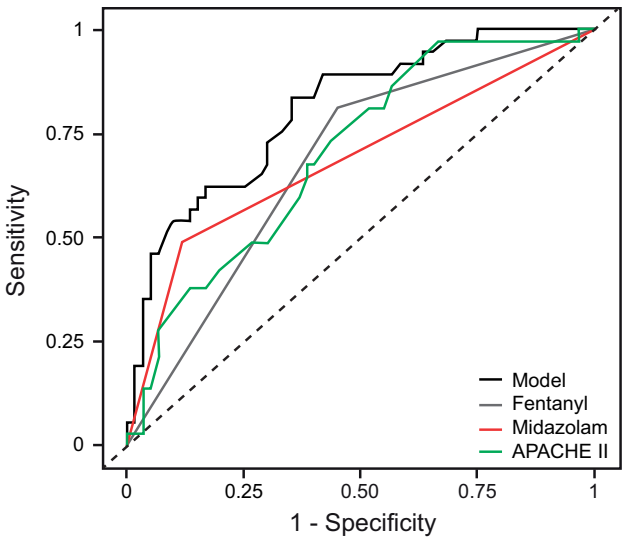

Fig. 1. Receiver operating characteristic curves of the entire model, midazolam, fentanyl, and Acute Physiology and Chronic Health Evaluation (APACHE II) score obtained when predicting re-intubation. Area under the curve for the entire model was 0.807. Area under the curve was 0.685 for midazolam, 0.680 for fentanyl use, and 0.704 for APACHE II score. APACHE II = Acute Physiology and Chronic Health Evaluation II.

COVID-19 who developed ARDS requiring invasive ventilation. In our cohort, 32% of subjects were re-intubated secondary to respiratory failure within 7 d of the first planned extubation. After controlling for significant variables in the univariate analysis, including postextubation respiratory support, comorbid conditions, and various sedatives, it was determined that APACHE II scores at ICU admission and midazolam or fentanyl use within 48 h prior to extubation were independently associated with re-intubation.

Researchers have investigated the risk factors and outcomes associated with extubation failure in other ICU populations.[6,16-20] Some of the most common variables identified were age, patient acuity, comorbid conditions, duration of ventilation, NMBA use, and positive fluid balance. Using benchmark data, our cohort had a higher re-intubation rate than reports from previous research in heterogeneous ICU populations (27% vs 10% at 96 h),[21] possibly related to the virus's complex and dynamic course. Determining the risk for re-intubation in specific demographic and diagnostic subgroups can assist clinicians in decision making before extubation. Unfortunately, there are limited data on re-intubation in invasively ventilated patients with viral illnesses. No pre-pandemic literature exists on the topic, and only 3 observational studies to date have investigated comprehensive risk factors for re-intubation among subjects with COVID-19.[8,11,12] However, no study to date has elucidated the risk factors for re-intubation secondary to respiratory failure in this cohort.

In a retrospective analysis of 281 adult subjects with the virus in the United States placed on invasive ventilation, Ionescu et al[8] found that 33% were re-intubated during the index hospitalization after planned extubation. The specific etiology for re-intubation was not described. Predictive factors for re-intubation included advanced age, vasopressor support requirement, renal replacement requirement, NMBA use, higher PEEP, and postextubation respiratory support. The authors found no correlation between re-intubation and sex, BMI, comorbid conditions, COVID-19 therapeutics, duration of ventilation, or pronation. Fleuren et al[11] examined re-intubation rates in 883 subjects with COVID-19 in the Netherlands who were intubated for > 24 h during hospitalization. The sample included subjects with both planned and unplanned extubations, but the specific etiology for re-intubation was not identified. Using machine learning, the researchers found re-intubation rates of 13.4% and 18.9% at 2 d and 7 d postextubation, respectively. After controlling for variables including demographics, lab values, comorbid conditions, sedative use within 24 h of extubation, and other variables, they identified ventilatory characteristics, inflammatory markers, neurological status, and BMI as predictors of failed extubation. Furthermore, Guzatti et al[12] performed a single-center, retrospective observational study in Brazil

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Table 6. Univariate Analysis for Mortality

Variable	OR	CI	*P*
Age	1.05	1.01–1.09	.009
Male	3.99	1.24–12.85	.02
BMI	0.95	0.90–1.01	.11
Race	0.89	0.62–1.26	.52
APACHE II score	1.04	0.98–1.08	.17
Positive CAM-ICU score	4.37	1.68–11.34	.002
Dominant variant by time frame	1.55	0.93–2.58	.09
Diabetes mellitus	2.86	1.04–7.83	.042
Hypertension	1.72	0.61–4.89	.30
Pulmonary disease	1.31	0.38–4.49	.66
Cardiac disease	1.69	0.57–4.98	.34
Chronic kidney disease	1.62	0.51–5.11	.41
Remdesivir	1.58	0.60–4.21	.36
Dexamethasone	2.96	0.92–9.54	.068
Tocilizimab	0.17	0.02–1.36	.10
Propofol	1.99	0.70–5.65	.20
Midazolam	1.94	0.71–5.32	.19
Fentanyl	3.09	0.961–9.950	.058
Ketamine	3.10	0.81–11.85	.10
Time from admission to first intubation	0.80	0.39–1.58	.50
Duration of initial mechanical ventilation	0.99	0.93–1.07	.90
Re-intubation	29.30	3.60–23.55	.002
Significant multivariate analysis for mortality			
Age	1.07	1.02–1.23	.005
Male	4.90	1.08–22.35	.041
Positive CAM-ICU score	5.43	1.58–18.62	.007
Re-intubated	12.75	2.80–57.10	< .001

OR = odds ratio
BMI = body mass index
APACHE II = Acute Physiology and Chronic Health Evaluation II
CAM-ICU = Confusion Assessment Method for the ICU

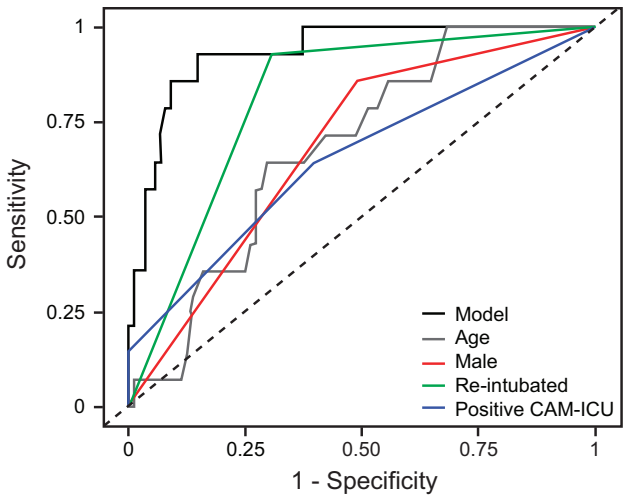

Fig. 2. Receiver operating characteristic curves of the entire model, subject age, male sex, re-intubation within 7 d, and positive Confusion Assessment Method for the ICU (CAM-ICU) score obtained when predicting mortality. Area under the curve for the entire model was 0.933. Area under the curve was 0.686 for subject age, 0.684 for male sex, 0.811 for re-intubation within 7 d, and 0.651 for positive CAM-ICU score. CAM-ICU = Confusion Assessment Method for the ICU.

with 77 intubated subjects with COVID-19, analyzing the potential risk factors for re-intubation in the ICU after planned extubation. The re-intubation rate was 22.1%. However, extubation failure was observed in only 7.8% of cases when evaluated 48 h after extubation. Specific causes for re-intubation were not identified. They identified age > 66 y, P_{aO_2}/F_{IO_2} < 200 mm Hg, need for dialysis, and > 31 d of symptoms as independent predictors of extubation failure. The authors did not include specific demographics, such as ethnicity, comorbid conditions, or mortality, in their analysis.

In our cohort, we found re-intubation rates higher than Fleuren et al[11] and Guzetti et al[12] and similar to Ionescu et al.[8] However, our rates could have been higher if we had used all-cause etiology and hospitalization as a definitional time frame. The concordance of results with Ionescu et al[8] could be related to research location, with both studies based in the United States, including heterogeneous subject populations and similar COVID-19 variants. The results of our research concur with the aforementioned studies regarding the lack of association between re-intubation and sex, comorbid conditions, and COVID-19 therapies. However, we did not find a correlation between re-intubation and age, BMI, NMBA use, postextubation respiratory support, or duration of ventilation. Inclusion and exclusion criteria, sample size, and data collection differed between our study and this research, possibly explaining some of the disparate findings. For example, the lack of association between re-intubation and duration of ventilation in our cohort may have been due to our exclusion criteria. We did not include subjects re-intubated for upper-airway obstruction, which research has shown to be associated with longer ventilation time and re-intubation.[22] Studies have shown that risk factors for re-intubation vary secondary to the cause.[23] Regarding BMI, fewer subjects in the Fleuren et al[11] cohort were obese compared to our study (33.6% vs 66%), and the authors analyzed data according to stratification of weight ranges. Due to incomplete data for certain subjects, we did not analyze ventilator settings or examine lab values (including blood gases) before extubation.

Unlike Fleuren et al,[11] we found a correlation between re-intubation and sedatives, with significant associations for midazolam and fentanyl use within 48 h prior to extubation. Some of the variations in results could be related to the exclusion criteria used in Fleuren et al,[11] which did not exclude unplanned extubation nor transfers within 24 h of extubation, in addition to the higher BMI of our cohort. According to a prospective observational study by Choi et al[24] investigating the pharmacokinetics of fentanyl in critically ill subjects, weight was the most crucial factor affecting fentanyl's total clearance and volume of distribution to the peripheral compartment. In addition, midazolam and its

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metabolites accumulate in obese patients through excess fatty tissue, increasing the risk for prolonged sedation and influencing clinical recovery.[25]

In other ICU populations, midazolam and fentanyl have been associated with extubation failure and an increased risk of delirium. Based on previous studies, delirium among ICU patients is related to multiple complications and adverse outcomes, including respiratory insufficiency, failed extubation, prolonged hospitalization, and increased mortality.[26] Mechanically ventilated patients with COVID-19 have elevated requirements for continuous, deep sedation and analgesia, resulting from a high respiratory drive, ventilator asynchrony, prone positioning, and an intense inflammatory response linked to the development of opioid tolerance.[27] According to a large international study investigating the prevalence and risk factors of delirium among the critically ill with COVID-19, approximately 55% of invasively ventilated patients with the virus developed delirium, with age, continuous opioid infusion, and benzodiazepine use associated with higher risk.[28] In addition, our cohort consisted exclusively of subjects with COVID-19 with ARDS. Research has shown that ARDS increases the risk of delirium compared to invasive ventilation without the syndrome, even after adjusting for illness severity and sedative use.[29] Our research showed more re-intubated subjects with a positive CAM-ICU score 48 h before extubation and within 7 d of ETT removal (58% vs 36%, $P = .033$), although this variable was insignificant for re-intubation when controlling for other factors in multivariate analysis.

Our study also demonstrated that APACHE II scores, used in other ICU populations to predict extubation failure,[30-33] were significantly higher among subjects who failed extubation. In our multivariate analysis, APACHE II scores were independently associated with re-intubation. However, sensitivity (42%) and specificity (11%) were poor for a cut-point of 28.0 determined using the Youden J Index, making this an inaccurate predictor variable. Our results differ from Fujii et al,[23] who found no association between APACHE II scores and re-intubation in the ICU, specifically for respiratory insufficiency, in 262 non–COVID-19 medical and surgical subjects. However, our study did not identify APACHE II scores as a predictor of mortality among our COVID-19 cohort, contrary to previous research.[34]

Morbidity and Mortality

Multivariate analysis showed that age, male sex, positive CAM-ICU scores 48 h before extubation and within 7 d post ETT removal, and re-intubation were independently associated with mortality, with adjustments for comorbid diabetes, dexamethasone, tocilizumab, fentanyl, and ketamine use.

The pathophysiology underlying the increased risk of poor outcomes in older patients is an area of active research. However, weaker immune defense, higher levels of pro-inflammatory cytokines, and reduced levels of angiotensin converting enzyme 2, which may offer protection against acute lung injuries caused by a viral infection, have been suggested to contribute to a higher risk of severity and mortality among the elderly infected with COVID-19.[35]

Furthermore, our study showed findings consistent with multiple observational and meta-analytic studies identifying the male sex as a strong predictor of death in hospitalized adults with COVID-19.[36,37] The SARS-CoV-1 epidemic showed an age-adjusted relative mortality risk for males of 1.62 (95% CI 1.21–2.16) in Hong Kong[38] and 3.10 (95% CI 1.64–5.87) in Singapore[39] compared to females. Similar findings were found in the MERS outbreak in Saudi Arabia, where 52% of males and 23% of females died.[40] Sex differences in innate and adaptive immune systems have been reported and may account for the female advantage in COVID-19. For example, females have more significant macrophage and dendritic cell activity, higher CD4+/CD8+ T-cell counts, CD8+ cytotoxicity, and greater immunoglobin production from B cells than males.[36,37]

We also found an association between positive CAM-ICU scores and mortality in our cohort. In a systematic review of 9 studies on COVID-19 ($N = 3,868$), Pranata et al[41] found that the presence of delirium was associated with increased mortality risk in older subjects with COVD-19 (OR 1.50 [95% CI 1.16–19.40], $P = .002$). Hariyanto et al[42] found similar results in a meta-analysis of 20 studies examining mortality risk from delirium in severe COVID-19 (OR 1.90 [95% CI 1.55–2.33], $P < .001$). In another systematic analysis of 48 studies ($N = 11,553$), Shao et al[43] found that delirium occurred in 33% of subjects with COVID-19 and was associated with a 3-fold increase in mortality. Rates of delirium increase with age,[42] but CAM-ICU scores were independently associated with death after controlling for age in our study. Older patients tend to have more comorbidities, but regression results for diabetes; hypertension; or a past medical history of pulmonary, cardiac, or chronic kidney disease were not significant in our cohort. Research has shown that delirium is associated with higher pro-inflammatory markers.[44] Wilson et al[44] speculated that the presence of delirium could be used as a marker for impaired peripheral perfusion and hyperinflammatory conditions, which may lead to higher death rates. Inflammatory lab values were inconsistently obtained in our cohort, with large numbers of incomplete data. Thus, we were unable to determine an association between these values and clinical outcomes. Delirium is known to occur based on sedative strategies, such as in the setting of benzodiazepine and opiate use. Our study found an independent association between re-intubation and mortality, and re-intubation was significantly associated with greater use of sedatives and analgesics. It is also possible that subjects

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who died were sicker (ie, pronated or required NMBA use), requiring titration to lower RASS scores, although rates of advanced treatments such as pronation and use of NMBA did not differ between groups. Furthermore, we did not collect the dosages of sedatives and opioids used by our cohort because of inconsistently recorded data in the electronic medical records. However, according to a systematic review of 14 studies[45] and multiple research studies,[46,47] the use of even small doses of benzodiazepines and opioids has been independently associated with an increased risk of delirium.

A significant increase in ICU and hospital LOS among re-intubated subjects was highlighted in our study. In our cohort, re-intubation was also independently associated with death. These findings were reported in studies on critically ill non–COVID-19 subjects who were re-intubated.[16-18] These outcomes are likely secondary to complications from the intubation process, mechanical ventilation, muscle weakness, and prolonged immobility. Thus, the reinstitution of invasive mechanical ventilation in patients with COVID-19 might have triggered discussions between the medical team and patients' families regarding goals of care and possible transitioning to palliative or comfort care.

We found higher mortality in our cohort with COVID-19–related ARDS re-intubated for respiratory failure (49% vs 3%). Our rate appears higher than values reported by Ionescu et al[8] (37%) and Fleuren et al[11] (1% at day 7), consistent with research showing more deaths in subjects re-intubated for non-airway problems, including respiratory failure.[6] In addition, our hospital is a tertiary-care center, and we accepted high-acuity patients with COVID-19 transferred from other hospitals for additional management when standard care failed.

Racial disparities in COVID-19 hospital mortality have also been reported, and our cohort was primarily comprised of minority subjects, with 57% Black and 28% Hispanic. Data from over 44,000 Medicare beneficiaries[48] showed that Black patients were more likely to die during hospitalization or be discharged to hospice than white patients (OR 1.11 [95% CI 1.03–1.19]), even after adjustments for individual patient characteristics, including age, sex, income, and comorbid conditions. Olanipekun et al[49] found that invasively ventilated Black subjects with COVID-19 were 3 times more likely to die in the ICU compared to white subjects (OR 3.1 [95% CI 1.6–5.5]), whereas Hispanic subjects were also at greater risk for death (OR 1.3 [95% CI 1.0–3.9]). Ricardo et al[50] found higher odds of 28-d mortality in Hispanic subjects (adjusted OR 1.44 [95% CI 1.12–1.84]) admitted to the ICU with COVID-19 compared with non-Hispanic white subjects, adjusted for age, sex, clinical characteristics, and hospital size. However, other studies have shown no racial differences in-hospital deaths from COVID-19.[51,52] From the literature, explanations for high mortality in minority patients with COVID-19 include quality of care related to hospital attributes,[48] social determinants of health, and more comorbidities in Black and Hispanic patients.[49] Although we did not find racial disparities between groups, our high death rate may reflect the demographic makeup of our cohort.

Limitations

Study limitations include a retrospective, observational design in a single-center with a relatively small sample size. Thus, our findings do not prove causation, and our ability to detect all relevant statistical differences may be limited. Furthermore, this study consisted mainly of minority subjects, with 85% of our cohort identified as non-Hispanic Black or Hispanic. Therefore, our study's findings may not apply to patient populations of other ethnicities.

In addition, we did not analyze ventilator settings, laboratory values, or sedative and analgesic dosages used during the ICU stay, which may be a potential source of confounding bias. We gathered our data using the electronic medical records, rendering data accuracy a potential source of bias. However, our results may spur future research to investigate the influence of certain factors, especially the impact of sedative and analgesic use, APACHE II, and CAM-ICU scores, in patients with ARDS secondary to a viral illness.

Conclusions

This study identifies several independent risk factors specific for re-intubation secondary to respiratory failure among subjects with COVID-19 with ARDS within one week of planned extubation. Results illustrated that midazolam and fentanyl use within 48 h prior to extubation and higher APACHE II scores at ICU admission are independently associated with re-intubation. Furthermore, our study demonstrated a re-intubation rate of 32%, which was higher than in heterogeneous ICU populations, and an association between positive CAM-ICU scores and increased mortality. In addition, we found that re-intubation was independently associated with higher mortality rates and correlated with prolonged hospital and ICU stays.

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