Predictors of intubation in COVID-19 patients undergoing awake proning in the emergency department

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ABSTRACT

Background: Awake prone positioning (PP) has been used to avoid intubations in hypoxic COVID-19 patients, but there is limited evidence regarding its efficacy. Moreover, clinicians have little information to identify patients at high risk of intubation despite awake PP. We sought to assess the intubation rate among patients treated with awake PP in our Emergency Department (ED) and identify predictors of need for intubation.
Methods: We conducted a multicenter retrospective cohort study of adult patients admitted for known or suspected COVID-19 who were treated with awake PP in the ED. We excluded patients intubated in the ED. Our primary outcome was prevalence of intubation during initial hospitalization. Other outcomes were intubation within 48 h of admission and mortality. We performed classification and regression tree analysis to identify the variables most likely to predict the need for intubation.
Results: We included 97 patients; 44% required intubation and 21% were intubated within 48 h of admission. Respiratory oxygenation (ROX) index and P/F (partial pressure of oxygen / fraction of inspired oxygen) ratio measured 24 h after admission were the variables most likely to predict need for intubation (area under the receiver operating characteristic curve = 0.82).
Conclusions: Among COVID-19 patients treated with awake PP in the ED prior to admission, ROX index and P/F ratio, particularly 24 h after admission, may be useful tools in identifying patients at high risk of intubation.

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1. Introduction

Acute respiratory distress syndrome (ARDS), or an ARDS-like illness, has been described among approximately one-third of hospitalized patients with COVID-19, and is thought to confer a high risk of mortality [1-6]. Patients often have a prolonged course of illness and require invasive mechanical ventilation (IMV) for long periods of time when intubated; this contributed to critical ventilator shortages in the early stages of the pandemic in the United States [2,4,7-9]. Patients undergoing IMV have been noted to have high mortality rates [6,8,10]. At the same time, early data suggest that patients who do ultimately require IMV may have worse outcomes when intubation is delayed [11-14]. The COVID-19 pandemic has thus confronted clinicians with the dual

challenge of identifying methods to avoid intubation in patients who can be managed without IMV, while preventing delays in intubation for those who need it.

COVID-19's unique disease pathology poses additional difficulties. The respiratory physiology of patients with respiratory distress or failure as a result of COVID-19 is heterogeneous. Prior studies have described continuum of ARDS-like illnesses, encompassing a form of "pseudoARDS," characterized by diffuse atelectasis and significant and rapid improvement in oxygenation and ventilation in response to positive pressure ventilation and prone positioning (PP), as well as a more traditional concept of ARDS characterized by poor compliance and prolonged recovery times [4,15,16]. PP, well studied for its benefit in intubated patients suffering from ARDS [17-21], has become a popular intervention for patients with COVID-19 who require intubation, as well as those capable of transitioning to PP while awake. The latter process has been referred to as awake PP [22-24]. The National Institutes of Health has recommended that awake PP be trialed among patients with

COVID-19 requiring supplemental oxygenation or noninvasive ventilation (NIV), but not used as rescue therapy for patients bordering on the need for intubation [25]. Awake PP has the potential to offer many of the same physiological benefits as traditional PP in the treatment of atelectasis, such as more homogenous transpulmonary pressures leading to decreases in volutrauma, barotrauma, and atelectotrauma; improved ventilation-perfusion matching; and improved clearance of secretions [22,26-29]. Moreover, awake PP requires fewer health care resources and limits staff exposure when compared to traditional proning of intubated patients [18].

Due to the novelty of the disease and the rapid evolution of treatment strategies, there is limited data regarding the efficacy of awake PP in hypoxic COVID-19 patients, and clinicians have little guidance to identify patients who are at high risk of failing awake PP. This is particularly troubling given the apparently blunted response of patients with COVID-19 to even severe hypoxia, which limits the utility of clinically observed "work of breathing" in assessing respiratory status [30]. Much of the available data is in the form of case series [31-43], and few of these studies examine the impact of early awake PP, implemented during patients' Emergency Department (ED) stay [44,45]. Likewise, many of these studies do not report clinically meaningful outcomes, such as intubation [46] or mortality rates [33,34,36,41, 42,44,46], and those that do have produced conflicting results [44,58].

In this retrospective chart review, we sought to identify the rate of intubation and IMV—both in the first 48 h of admission and over the course of hospitalization—among a group of patients with hypoxia due to COVID-19 treated with awake PP in the ED, and to identify clinical characteristics that may predict the need for intubation among this cohort.

2. Methods

2.1. Study setting

This was a multicenter retrospective study of patients admitted through the EDs of University of Maryland (UM) Prince George's Hospital Center, UM Laurel Regional Hospital, and UM Bowie Health Center, in Prince George's County, Maryland. Cases included were from patients admitted between March 12,020 and February 182,021. All 3 sites are part of the UM Capital Region Health. Prince George's Hospital Center is a 205-bed community hospital with a volume of approximately 42,000 ED visits per year. Laurel Regional Hospital expanded from a free-standing ED with 28,000 annual visits to a 135-bed hospital exclusively for patients with COVID-19 in April 2020 as part of SMaryland's state-level pandemic response. Bowie Health Center is a free-standing ED with an annual volume of approximately 32,000 visits.

Throughout our study period, hypoxic patients with suspected COVID-19 were provided with a one-page handout explaining the benefits of awake PP and instructions on how to self-prone while in the ED (Appendix 1). This handout instructed patients to rotate through 4 different positions, spending 30 min to 2 h in each: prone position, right lateral decubitus, seated at an incline of 30°-60° (semi-Fowler position), and left lateral decubitus. This awake PP protocol aligns with recommendations by the Intensive Care Society [22]. In addition, nurses and respiratory therapists cued patients to change position every 2 to 4 h during the day. Patients requiring low-flow oxygen, high-flow nasal cannula (HFNC), or NIV were maintained on oxygen and NIV support while in the prone position. The same protocol was available and encouraged in the inpatient units in Site A and Site B; however, the utilization of this protocol was left to the discretion of the attending hospitalist or intensivist, without specific hospital-wide indications for continuation.

During the timeframe of our investigation, convalescent plasma was available to ICU physicians at our institution on special request. Remdesivir was available for compassionate use among patients on the hospital wards or in the ICU. Steroids were recommended for the treatment of COVID-19 approximately halfway through our study period, and were included as a part of routine care thereafter. Similarly, hydroxychloroquine was used routinely over the first five months of our study period, after which its use was no longer recommended and was discontinued.

2.2. Selection of participants

Our study population included adult patients with confirmed or clinically suspected active COVID-19 infection admitted through the EDs of all three sites and who underwent awake PP in the ED. Records were reviewed for all patients who had a proning order placed in their electronic medical record (EMR). Emergency physicians were encouraged to place this order for patients with clinically suspected COVID-19 infection who required supplemental oxygen or NIV. After the initial records review, we included patients whose clinical presentation and course was considered consistent with COVID-19. Infection was verified via reverse transcription polymerase chain reaction (PCR) or nucleic acid amplification (NAA) testing performed on a nasopharyngeal specimen or, rarely, endotracheal aspirate or based on typical laboratory markers, imaging findings, and clinical characteristics.

We excluded patients if either their ED records or inpatient records were unable to be located. We excluded patients who required IMV or who expired during their initial ED evaluation. Pregnant patients, incarcerated patients, and pediatric patients (as defined by age less than 18 years) were also excluded from our study.

The study was approved by the institutional review board and the research review committee at the authors' institutions.

2.3. Data collection

We used a standardized Access database (Microsoft) as our data collection tool. Initial data were collected by a total of 6 authors; each patient's data was entered by one author and reviewed separately by a second. Any disagreements were adjudicated through discussion among the authors and the principal investigator. Patient data were obtained by reviewing the ED and inpatient EMRs.

We collected data on patients' past medical and surgical history, tobacco use, initial vital signs, laboratory values, and chest x-rays (CXRs), as well as the degree of supplemental oxygen or ventilatory support required, and their treatment course, including the use of concomitant therapies such as convalescent plasma, antivirals, steroids, and antibiotics. CXRs were evaluated using the severe acute respiratory infection (SARI) CXR scoring system [47], which classifies CXRs as either normal (assigned a score of 1) or characterized by patchy atelectasis, bronchial cuffing, and/or hyperinflation (2); focal alveolar consolidation isolated to one segment or lobe (3); multifocal consolidation (4); or diffuse alveolar consolidation (5). This approach has been internally validated to demonstrate good interrater reliability across a range of medical specialties and training levels and serve as an appropriate proxy for radiologist interpretation of CXRs [47]. CXRs obtained in the ED and on the first day of each patient's hospitalization were independently scored by 2 of the authors. We referred to radiologists' interpretation of CXRs to adjudicate any disagreements.

2.4. Primary clinical variables

We evaluated several clinical indicators to identify potential predictors of intubation, including the change in the ratio of partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2)—henceforth referred to as P/F ratio—and ROX (respiratory oxygenation) index (ratio of oxygen saturation [SpO2]/FiO2 to respiratory rate) [48-51]. The ROX index is a clinical decision aid used to predict failure of HFNC and need for intubation based on respiratory rate, SpO2, and FiO2 [49,50]. P/F ratio is a representation of oxygenation traditionally used to both diagnose and determine the severity of ARDS. We identified the P/F

ratio and ROX index, both at ED triage and 24 h after admission, as well as patient's age, laboratory markers previously shown to correlate with disease severity in COVID-19 [52], and evolution of pulmonary infiltrates on CXR within the first 24 h of hospitalization. "Initial" ROX index and P/F ratio reflect triage vitals and/or arterial blood gas (ABG) analyses obtained during the patient's initial ED assessment. When ABG results were not available, PaO2 was calculated from SpO2 [53]. For patients on low-flow supplementary oxygen, FiO2 was calculated from the flow rate [53].

2.5. Outcome measures

Our primary outcome was the intubation rate at any point during hospitalization. We also examined intubation during the first 2 days of hospitalization and survival to hospital discharge.

2.6. Statistical analysis

We first used descriptive analyses to compare demographic and clinical characteristics between patients who required intubation and those who did not. We present continuous data with mean ($\pm$ standard deviation [SD]) or median (interquartile range [IQR]) as appropriate, and categorical data using percentages. We used the student t-test and Mann-Whitney U test to compare continuous data and Chi-square test for categorical data.

We identified variables associated with intubation using classification and regression tree (CART) models, which have been shown to be particularly robust for data sets with outliers and missing variables [54,55]. For our CART analysis, we used a 10-fold cross-validation technique to evaluate variables as potential predictors (Appendix 2). The CART model creates a decision tree by performing recursive partitioning to identify a series of dichotomous splits (e.g., the need of intubation or not), and then examines each independent variable in order to maximize the sensitivity and specificity of each classification. The tree ends in "terminal nodes," which identify the final branch points significant to the outcome of interest. The model then assigns the single most important classification (that is, the predictor that is most strongly associated with the outcome of interest) the "relative variable importance" of 100%. The values assigned all other variables, also expressed as percentages, reflect the relative importance of those variables compared to that of the previously identified single most important classification. We considered all variables achieving a relative variable importance greater than 50% to be "important" predictors of intubation.

We reported the sensitivity and specificity of these predictors, and the goodness-of-fit of the CART model, via area under the receiver operating characteristic curve (AUROC) analysis. As AUROC approaches 1, the goodness-of-fit model improves. Using the continuous variables identified as important by our CART analysis, we carried out probit and logit regressions to identify the probability that a patient would require intubation at any particular level of each continuous independent variable (for example, any given P/F ratio or ROX index). We considered all results with 2-tailed P values <0.05 to be statistically significant. We used Minitab version 19.0 (Minitab, LLC) and Stata version 15.0 (StataCorp) for our statistical analyses.

3. Results

3.1. Demographics and patient characteristics

Our study included a total of 98 patients hospitalized for COVID-19 who underwent awake PP during their ED stay (Appendix 3). Sixty-one percent were males. The mean age was 54 (SD 14) and mean body mass index (BMI) was 31, with 57% of patients identified as obese (BMI ≥ 30). Sixty-eight percent had underlying medical comorbidities, the most common of which were hypertension (43%) and diabetes (33%). Patients requiring IMV were more likely to have a chronic

comorbid condition (82% compared to 61%, $P < 0.05$), and to have diabetes (47% compared to 24%, $P < 0.05$) (Table 1).

At the time of admission, 89% of participants required supplemental oxygen to maintain a goal SpO2 > 90%, 42% on NC with a median flow of 3 L and 48% on HFNC at a median of 30LPM and FiO2 90%. Awake PP was continued in the hospital for 63% of patients who ultimately required IMV in contrast to approximately 25% of patients who did not require IMV.

3.2. Primary outcome: rate of intubation during hospitalization

Of our cohort, 44% required intubation and mechanical ventilation during their hospital stay. Patients who were intubated had significantly worse respiratory indicators on arrival to the ED and 24 h into their hospital stay (Table 1). These patients were more likely to have required higher levels of oxygen support on arrival to the ED. Both initial and repeat P/F ratios were significantly lower in the intubated group: the median initial P/F ratio among patients who required intubation was 180 (IQR 96, 238), compared to 286 (IQR 221, 329) among those who did not ($P < 0.01$). After 24 h, the median P/F ratio among patients who required intubation was 109 (IQR 73, 174), compared to 255 (IQR 280, 363) among those who did not ($P < 0.01$).

Patients ultimately requiring IMV had significantly lower initial and repeat ROX indices. The median initial ROX index among patients who required intubation was 9.9 (IQR 4.0, 13.5), compared to 15.9 (IQR 11.5, 20.4) among those who did not require intubation ($P < 0.01$). After 24 h, the median ROX index among patients who required intubation was 4.6 [IQR 3.0, 7.9], compared to 15.7 [IQR 8.2, 18.5] among those who did not ($P < 0.01$).

The mortality rate of patients requiring intubation was 47%, compared to 0% among those who did not (Table 1). Two patients were transferred to another facility for treatment with VV-ECMO, both of whom survived.

3.2.1. Predictors of intubation during hospitalization

Using CART analysis, we identified P/F ratio at 24 h after admission as the most important parameter in predicting need for intubation and IMV at any point in the patient's hospitalization, followed by ROX index and CXR score at 24 h (Fig. 1). Eighteen percent of patients with a CXR score of 4.5 were intubated throughout their hospitalization (Terminal Node 1; Fig. B). Among patients with a CXR score > 4.5, procalcitonin was identified as a significant interaction, with P/F ratio and ROX index at 24 h resulting in terminal nodes. Among patients with a low (</=0.15 ng/mL) procalcitonin level, those with a P/F ratio of £ 169 at 24 h faced a hospital intubation rate of 56% (Terminal Node 2; Fig. B), while none with a P/F ratio of >169 required intubation (Terminal Node 3; Fig. B). Among those with a higher (>0.15 ng/mL) procalcitonin level, a ROX index at 24 h of £ 9.7 was associated with a hospital intubation rate of 89% (Terminal Node 4; Fig. B), in contrast to 13% of those with a ROX index >9.7 (Terminal Node 5; Fig. B). Our AUROC model reported an area under the curve >0.8 and $P < 0.001$ for 24-h ROX index, P/F ratio, and 24-h CXR score. Sensitivity and specificity were both >70%.

Probit and logit analysis suggests that 24-h ROX index values of 9.7, 6.87, and 4 might be expected to confer a 35%, 50%, and 65% probability, respectively, of intubation during hospitalization (Fig. 2A). We subsequently identified a 24-h P/F ratio of 148 as expected to confer a 50% probability of intubation (Fig. 2B).

3.3. Secondary outcome: intubation within 48 hours of admission

Fifty-five percent of patients who required IMV were intubated within the first 48 h of hospitalization. Demographic variables were not significantly different between patients requiring intubation in the first 48 h of admission and those requiring later intubation, with the exception of a higher prevalence of DM in the early intubation group

Table 1

Demographic and clinical characteristics, treatments, and outcomes of patients treated with awake PP in the emergency department for hypoxia due to COVID-1.

	Intubated n = 38 (44%)	Not intubated n = 59 (56%)	P value[a]
Demographics			
Age, mean (SD), y	58 (2)	51 (2)	0.12
Sex, n (%)			0.52
Male	25 (66)	35 (59)	
Female	13 (34)	24 (41)	
BMI, n (%)			
<30	18 (47)	23 (39)	0.32
30–40	11 (29)	26 (44)	
>40	9 (24)	10 (17)	
Race/ethnicity, n (%)			0.29
African American	16 (42)	33 (56)	
Hispanic	3 (8)	6 (10)	
Other	19 (50)	20 (34)	
Clinical characteristics			
Past medical history, n (%)			
Any chronic condition[b]	31 (82)	36 (61)	<0.05
Asthma	3 (8)	4 (7)	0.84
CHF	2 (5)	5 (8)	0.55
CAD	0 (0)	4 (7)	0.10
DM	18 (47)	14 (24)	<0.05
COPD	2 (5)	3 95)	0.97
Hyperlipidemia	5 (13)	11 (19)	0.48
Hypertension	18 (47)	24 (41)	0.52
CKD	3 (8)	4 (7)	0.84
Initial shock index, n (%)[c]			
<1	31 (82)	52 (88)	0.37
≥1	7 (18)	7 (12)	
Initial laboratory values			
Creatinine (mg/dL), median (IQR)	0.95 (0.7, 1.1)	0.9 (0.7, 1.2)	0.48
ALC (103/mcL), median (IQR)	9.1 (6.8, 11.7)	8.4 (6.2, 10.6)	0.19
CRP (mg/L), median (IQR)	196 (146, 301)	127 (60, 214)	<0.05
D-dimer (mcg/mL FEU), median (IQR)	0.92 (0.72, 1.31)	0.76 (0.58, 1.23)	0.16
Ferritin (ng/mL, median (IQR)	696 (350, 1500)	841 (459, 1425)	0.33
Additional therapies			
Pharmacologic therapies used, n (%)			
Azithromycin	30 (79)	33 (56)	<0.05
Convalescent plasma	12 (32)	12 (20)	0.21
Dexamethasone	15 (40)	24 (41)	0.91
Hydroxychloroquine	9 (24)	9 (15)	0.30
Remdesivir	11 (29)	21 (36)	0.50
Indicators of respiratory status			
Initial O2 delivery device, n (%)			
Room air	19 (50)	41 (70)	<0.05
Nasal cannula	5 (13)	13 (22)	
Non rebreather	14 (37)	5 (9)	
Initial P/F ratio, n (%)			
>300	6 (16)	23 (39)	<0.01
200–300	10 (26)	26 (44)	
<200	22 (58)	10 (17)	
P/F ratio at 24 h, n (%)			
>300	2 (5)	20 (34)	<0.01
200–300	5 (13)	19 (32)	
<200	31 (82)	20 (34)	
Change in P/F ratio, median (IQR)	+64 (−18 to 128)	+29 (−48 to 96)	<0.01
Initial ROX index, median (IQR)	10 (4, 14)	16 (12, 20)	<0.01
>4.88	25 (66)	53 (90)	<0.05
3.85–4.88	5 (13)	3 (5)	
<3.85	8 (21)	3 (5)	
ROX index at 24 h, n (%)			
>4.88	18 (47)	51 (86)	<0.01
3.85–4.88	5 (13)	3 (5)	
<3.85	15 (40)	5 (9)	
Change in ROX index, median (IQR)	4.6 (−0.78, 9.6)	1.9 (−3.6, 6.40	<0.01
CXR grade on admission, n (%)[c]			
1 to 3	5 (13)	23 (39)	<0.05
4 or 5	32 (84)	32 (54)	

(continued on next page)

Table 1 (*continued*)

	Intubated n = 38 (44%)	Not intubated n = 59 (56%)	P value[a]
Admission status and outcomes			
Admission level of care, *n* (%)			<0.01
Floor	16 (42)	50 (85)	
ICU	22 (58)	9 (15)	
Mortality, *n* (%)	18 (47)	0 (0)	<0.01

Abbreviations: ALC, absolute lymphocyte count; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CXR, chest x-ray; D-dimer, dimerized plasmin fragment D; DM, diabetes mellitus; ED, emergency department; FEU, fibrinogen equivalent units; ICU, intensive care unit; IQR, interquartile range; O2, oxygen; P/F, partial pressure of oxygen/fraction of inspired oxygen; PP, prone positioning; ROX, respiratory oxygenation; SD, standard deviation.

[a] *P* values generated using Student *t*-test, Mann-Whitney U test, or Chi-square test.

[b] "Any chronic condition" includes a diagnosis of any of the chronic diseases listed below, as well as HIV and malignancy.

(Supplemental Table 1). Respiratory parameters were significantly different between these groups. Patients requiring early intubation had a significantly lower median initial ROX index (4.5, IQR 2.9, 10.9) than those intubated later in their hospital course (12.5, IQR 9.9, 18.5) as well as a lower initial P/F ratio (139.4, IQR 76.8, 209.1 compared to 223.8, IQR 161.9, 347.6, *P < 0.05*). Forty-eight percent of those requiring intubation within the first 48 h survived to hospital discharge, compared to 59% of those intubated later in their hospital course.

(a)

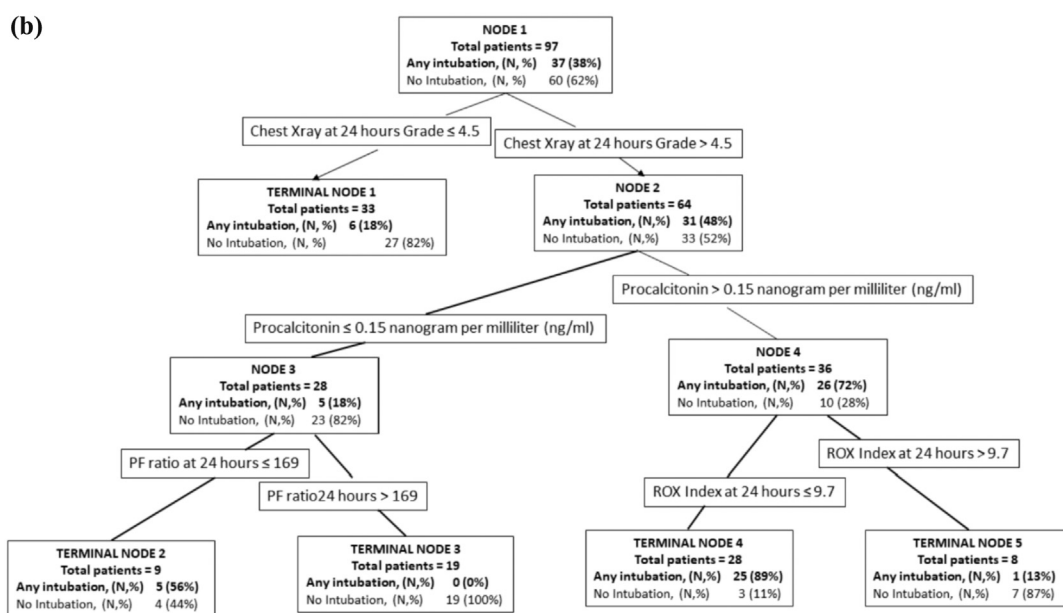| Variables	Relative Variable Importance (%)	AUC	95%CI	Sensitivity	Specificity	P
PF ratio at 24 hours	100	0.82	0.73-0.89	70	86	0.001
ROX index at 24 hours	92	0.82	0.73-0.89	72	88	0.001
CXR Grade at 24 hours	89	0.81	0.6-0.94	81	87	0.001
Procalcitonin	70	0.79	0.65-0.9	81	71	0.001
PF ratio at triage	61	0.73	0.63-0.81	76	72	0.001
CRP	46	0.73	0.61-0.83	81	65	0.001
D-Dimer	26	0.61	0.5-0.72	63	64	0.079
CXR Grade at 48 hours	23	0.57	0.29-0.80	100	22	0.69
ROX index at triage	21	0.73	0.64-0.82	76	65	0.001
PF ratio change at 24 hours	20	0.6	0.49-0.70	66	55	0.11
CXR Grade at triage	17	0.67	0.56-0.77	69	63	0.001
Receiving Azithromycin	15	0.6	0.5-0.71	78	43	0.02
WBC	13	0.59	0.49-0.69	73	47	0.14
Ferritin	10	0.58	0.45-0.69	41	79	0.29

(b)

Fig. 1. A. Relative variable importance and area under the operator receiving curve analysis of important predictors for any intubation *during hospitalization* among patients with COVID-19 treated with awake PP in the emergency department. Only predictors with relative variable importance ≥10 were reported. B. Classification and regression tree (CART) analysis tree diagram identifying the most important variables for predicting need for intubation *during hospitalization*.
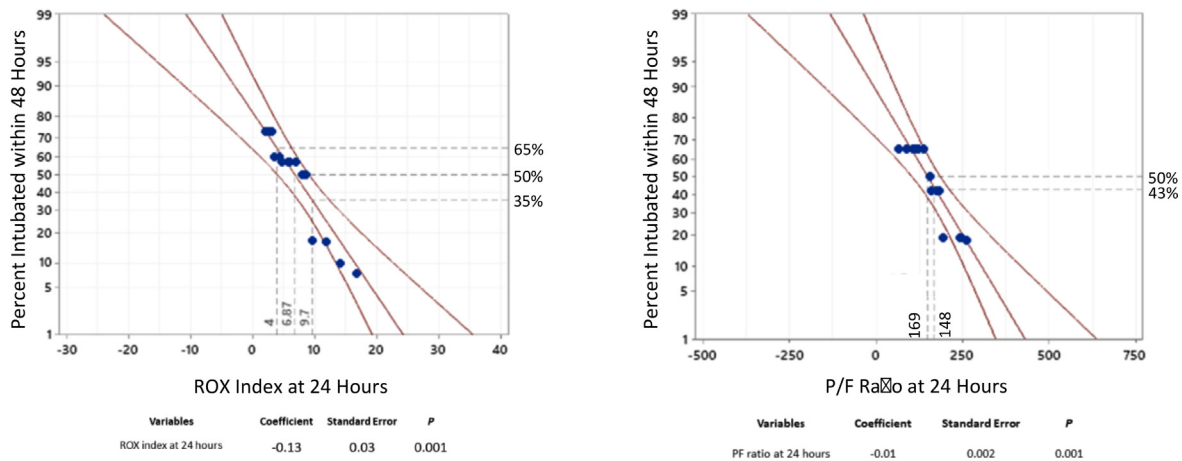
Fig. 2. Probit analysis for probability of intubation during hospitalization associated with important relative variables (ROX index at 24 h and PF ratio at 24 h).

3.3.1. Predictors of intubation: within 48 hours of admission

We identified ROX index at 24 h after admission as the most important variable in predicting need for intubation within the first 48 h of hospitalization, followed by ROX index at triage and P/F ratio at 24 h (Fig. 3). While not identified as one of the most important variables, P/F ratio at triage was 85% sensitive in predicting need for intubation within 48 h (Fig. 3), with an area under the curve of >0.8 and $P <$ 0.001. Thirty-eight percent of patients with a 24-h ROX index of ≤11.8 required intubation within 48 h of admission (Terminal Node 1; Fig. B), compared to none with a 24-h ROX index >11.8 (Terminal Node 2; Fig. B). Our AUROC model reported an area under the curve >0.8 and $P <$ 0.001 for ROX index at 24 h, ROX index at triage, and P/F ratio at triage.

Probit and logit analysis suggests that patients with a ROX index of 5 or P/F ratio of 81 at triage (Fig. 4A and B) have a 50% probability of requiring intubation within the first 48 h of hospitalization. Similarly, patients with a ROX index of 2 or P/F ratio of 54 at 24 h after admission faced a 50% likelihood of requiring intubation within 48 h of hospitalization (Fig. 4C and D).

4. Discussion

Our study found a high rate of intubation and IMV during hospitalization, measured at 44%, in patients admitted to the hospital for COVID-19 who were treated with awake PP during their ED stay. Lower ROX indices and P/F ratios were associated with increased rates of intubation

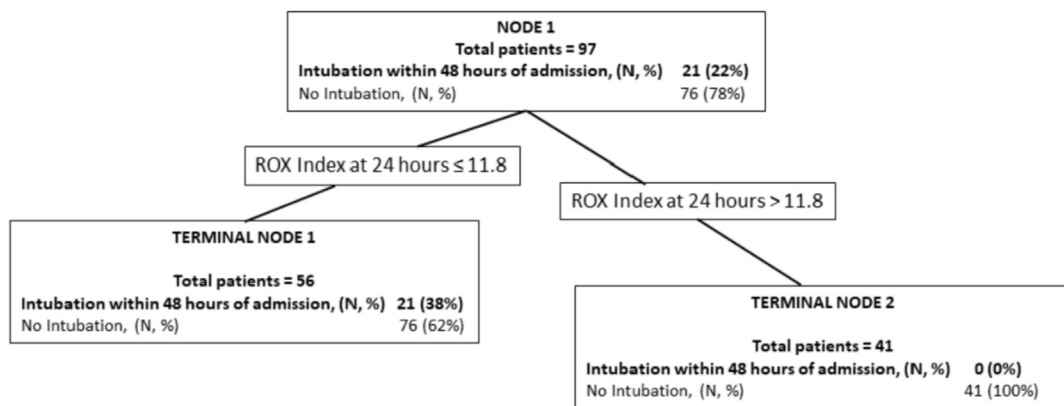| Variables	Relative Variable Importance	AUC	95%CI	Sensitivity	Specificity	P
ROX index at 24 hours	100	0.81	0.71-0.88	94	62	0.001
ROX index at triage	90.2	0.84	0.75-0.90	76	77	0.001
PF ratio at 24 hours	90	0.78	0.75-0.91	95	61	0.001
PF ratio at triage	68	0.8	0.70-0.87	85	68	0.001
CXR Grade at 24 hours	32	0.79	0.58-0.92	84	72	0.001
D-Dimer	32	0.64	0.52-0.75	76	51	0.044
ROX index change in 24 hours	28	0.52	0.41-0.62	50	72	0.8
CXR Grade at 48 hours	25	0.58	0.31-0.81	100	17	0.57
PF ratio change at 24 hours	17	0.52	0.41-0.62	42	76	0.78
CRP	13	0.67	0.55-0.78	71	65	0.03

Fig. 3. A. Relative variable importance and area under the operator receiving curve's analysis of important predictors for intubation *within 48 h of admission*. Only predictors with relative variable importance ≥10 were reported. B. Classification and regression tree (CART) analysis decision tree identifying the most important variables for predicting need for intubation *within 48 h of admission*.
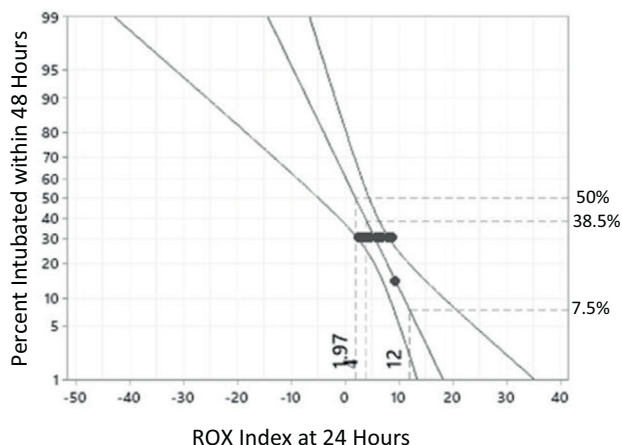
A. ROX index at Triage
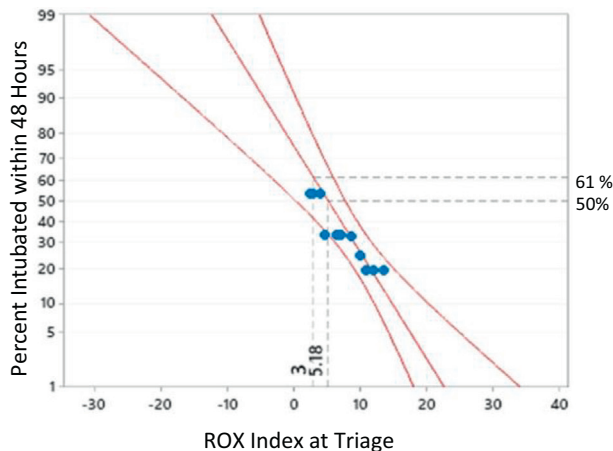
B. P/F Ratio at Triage

Variables	Coefficient	Standard Error	P
Triage ROX index	-0.13	0.03	0.001
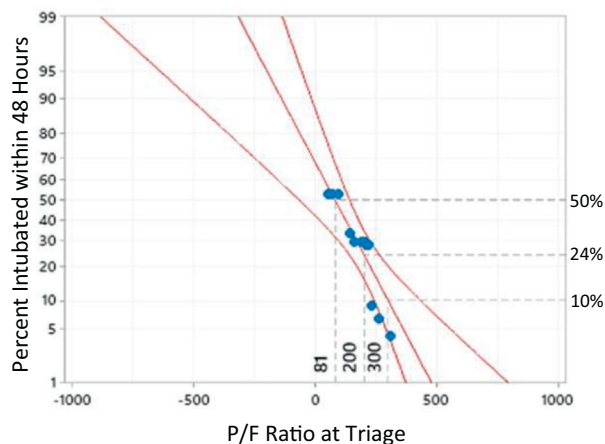
Variables	Coefficient	Standard Error	P
Triage PF ratio	-0.006	0.001	0.001

C. ROX index at 24 Hours

D. P/F Ratio at 24 Hours

Variables	Coefficient	Standard Error	P
ROX index at 24 hours	-0.14	0.04	0.001
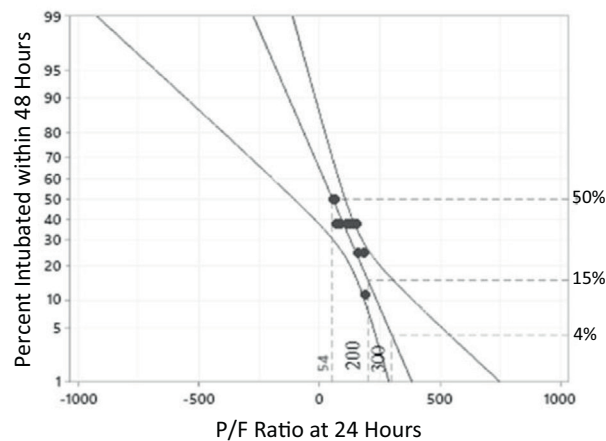
Variables	Coefficient	Standard Error	P
PF ratio at 24 hours	-0.007	0.002	0.001

Fig. 4. Probit analysis for probability of intubation within 48 h of hospitalization associated with important relative variables.

in our patient population. Over half of patients requiring IMV were intubated within the first 48 h of their hospitalization.

Our observations are consistent with the findings of other published observational cohort studies of patients with COVID-19 who were treated with awake PP. These studies reported intubation rates varying from 10% to 58% [44,45,56-58]. The rate of intubation among our cohort is similar to those reported by other studies conducted specifically in the ED [44,45]. It is on the higher end of others conducted in the United States (both in the ED and on inpatient units), which reported rates ranging from 10% to 48%. The time frames over which intubations were included in these studies is not always clear [32,44,57,58]. Our cohort was similar to those described in these other studies with respect to age, initial P/F ratio, and initial ROX index. Patients who ultimately required intubation and IMV were more likely to require higher levels of

oxygen support on ED arrival and had significantly worse respiratory indicators, both on ED arrival and 24 h later.

We found that CXR score, ROX index, and P/F ratio at 24 h were important variables in identifying patients at high risk for intubation during their hospitalization. The AUROC for the ROX index at 24 h in our study was comparable to that in the original validation studies of the ROX index as a predictor for intubation among patients on HFNC [49,50]. In the absence of other indicators, both ROX index and P/F ratio may prove to be valuable tools in identifying patients who may require or benefit from early intubation, particularly among the so-called "happy hypoxemics," who do not demonstrate the clinical symptoms expected among patients in respiratory distress [30].

Both our and the validation studies found that the ROX index was more useful at 24 h than at the time of presentation. In our study,

both ROX index and P/F ratio had greater prognostic value at 24 h than at triage, both with respect to intubation at any point during the hospitalization, as well as intubation within 48 h of admission. We did, however, find that ROX index at triage was an important indicator of intubation within 48 h of admission, and P/F ratio at triage had good sensitivity (85%) in identifying patients with a high likelihood of early intubation. This suggests that while Emergency Medicine physicians should exercise caution with respect to early prognostication among patients requiring even high levels of supplemental oxygen in the ED, these tools ay be useful in identifying patients at high risk of early decompensation.

The ROX index was developed and validated specifically among patients undergoing treatment with HFNC, while we have applied it more broadly in this study to any COVID-19 patient requiring hospitalization. The ROX index has not been investigated specifically among patients with COVID-19. Our analysis suggests that it may be a valuable predictor of intubation in this patient population, but that the interpretation of the index may need to be adjusted. Previously, patients treated with HFNC with a ROX index >4.88 were considered at low risk for intubation [49,50]. Conversely, among our patients with respiratory failure due to COVID-19, a similar index was associated with a probability of intubation greater than 50%. There are several factors that may have influenced our findings. Clinicians in our facilities may have had a lower threshold for intubation when caring for patients with COVID-19 than for other etiologies of respiratory failure. The difference could also suggest that COVID-19 infection is associated with a different and more severe mechanism of respiratory distress, causing patients to require intubation at a higher ROX index. It has been suggested that patients with respiratory failure induced by COVID-19 may have a blunted response to hypoxia; such a response may impact how their respiratory status is represented by the ROX index. Further studies are needed to validate whether the ROX index is applicable in patients with COVID-19, and how it should be interpreted when caring for these patients.

Our results highlight the promise of both ROX index and P/F ratio as potential tools to assess risk of intubation in hospitalized patients with COVID-19. In our patient population, these measurements of oxygenation, oxygen support, and work of breathing were found to be more important predictors of intubation than patient demographics, BMI, comorbidities, or laboratory values. The decision to intubate is always complex and takes into account a number of dynamic variables that are not adequately captured in our study or any clinical decision tool, such as mentation, subjective and observed work of breathing, perfusion status, overall clinical picture, and perhaps available resources. However, given the unique and novel clinical picture and spectrum of respiratory failure from COVID-19, and the evidence of poor outcomes associated with delayed intubation, we anticipate that the development of tools to aid in this decision would improve patient care [12,13].

4.1. Implications for future research

Our investigation suggests that awake PP in ED patients with COVID-19 is feasible. Additional studies with large sample sizes and robust control groups are needed to confirm and quantify the benefit of this practice with respect to intubation rates and mortality. Because this practice has been described as a tactic used to prevent intubation, it is essential that the clinician be able to identify patients at high risk of failing awake PP when choosing whether to implement early IMV or observe patients. Our analysis identifies P/F ratio and the ROX index as potentially useful tools to identify patients at high risk of intubation despite awake PP. Additional research is needed to validate this association and identify the potential threshold for each tool that should prompt clinicians to consider early intubation, and to examine how these variables

should be expected to change over time in patients treated with awake PP. Finally, additional investigations are needed to identify the clinical outcomes associated with early versus late intubation among patients with COVID-19, and the role of awake PP in the care of these patients.

4.2. Limitations

This was a retrospective, observational study of a relatively small cohort. The absence of a control group prevents us from isolating the impact of awake PP on intubation rates, and from determining whether our predictors of intubation apply differently to patients who have undergone awake PP versus those who have not. Although the patients included in our study were admitted and treated in three different EDs, our study was limited to a single healthcare system; there may be specific admitting and clinical practices (for example, thresholds for the initiation of NIV or intubation and availability of HFNC) that limit the application of our results outside of this setting. Furthermore, our study did not control for all events during the patient's hospitalization that may have influenced patient outcomes, such as the continuation of awake PP during hospitalization, which occurred in approximately one third of our sample, the volume of fluid resuscitation provided and risk for volume overload, and the development of hospital-acquired venous thromboembolism or pneumonia. Finally, the patients included in our study were hospitalized between March 2020 and February 2021, a highly volatile time period in the treatment of COVID-19 during which both our understanding of the disease and the available, recommended therapeutic strategies evolved rapidly [59]. Any comparison of outcomes among patients treated early in the pandemic with those treated more recently should be undertaken with great caution.

5. Conclusion

Our investigation adds to the growing body of data regarding outcomes of patients with COVID-19 treated with awake PP. Furthermore, we provide early insights into possible clinical decision tools, such as 24-h ROX index and P/F ratio, to help identify patients at high risk of intubation, both shortly after admission and throughout their hospital course, which may help determine appropriate level of care and avoid delayed intubations. Further investigations are needed to validate the values for each index used to guide such decisions.

Authors' contributions

Conceptualization: QKT, BS, JD, SC, RA, SS, AD
Data collection: JD, SC, RA, SS, AD, RP, BS
Data analysis: QKT, BS, PB
Manuscript preparation: JD, SC, RA, QKT, BS
Critical revision of manuscript: JD, SC, RA, QKT, BS, SS, AD, RP, PB

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix 1

Awake Proning
Patient Self-Care Guide

**Awake Proning is a patient driven process.
It has been used since the 1970s to help patients with respiratory problems.**
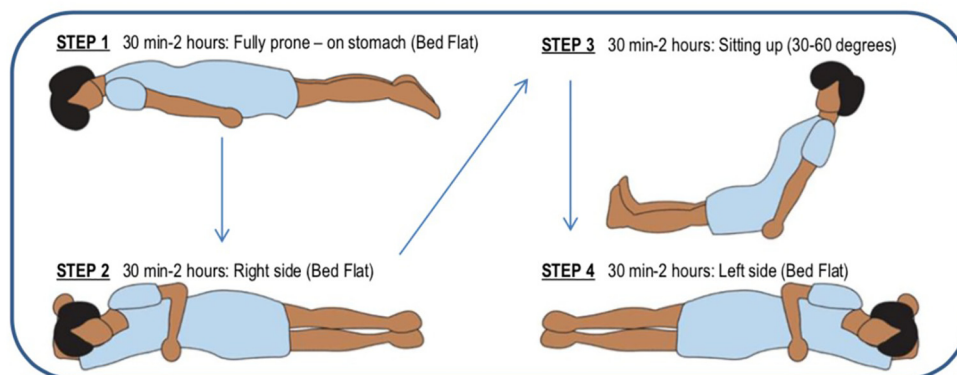
The benefits of Awake Proning are:

- Improved secretion clearance (gravity works in your favor)
- Improves lung function while allowing your oxygen levels to rise
- Helping the oxygen levels to rise allows your lungs to recover

Safety Precautions:

- If using oxygen, be aware of tubing so that:
  - There is adequate tubing length to allow you to turn
  - The tubing does not get kinked, cutting off the oxygen flow
  - The tubing does not get tangled
- Use pillows as needed to support your body
- Ensure your safety by making certain your top side rails are in the up position while in the hospital; or you are far enough from the edge of the bed when at home

Procedure for Awake Proning:

- Follow the STEPS below, rotating your position every 30 minutes to 2 hours. (see figures below)
- Repeat STEPS 1-4, positioning per your comfort level

STEP 1 30 min-2 hours: Fully prone – on stomach (Bed Flat)

STEP 3 30 min-2 hours: Sitting up (30-60 degrees)

STEP 2 30 min-2 hours: Right side (Bed Flat)

STEP 4 30 min-2 hours: Left side (Bed Flat)

NOTE: Stop the Awake Proning if you are unable to tolerate this activity.
Inform your nurse of any distress if you are in the hospital.

Not recommended if you have frequent seizures or are pregnant.

Fig. A-1. One-page handout provided to patients explaining the benefits of awake prone positioning and instructions on how to self-prone.

Appendix 2

Variables used in CART analysis.

Mode of ED arrival	History of COPD
Chief complaint	History of CKD
Time of arrival	Smoking status
Age	Creatinine
Sex	WBC
Race	ALC
Ethnicity	AST
BMI	ALT
Initial shock Index	Troponin
Initial ROX index	Lactate
Initial P/F ratio	D-dimer
Initial qSOFA score	Procalcitonin
History of CAD	Ferritin
History of DM	Triage CXR score
History of HTN	ROX index at 24 hours
History of HLD	P/F ratio at 24 hours
History of CHF	24-hour change in ROX index
History of asthma	24-hour change in P/F ratio

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; CART, classification and regression tree; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; D-dimer, dimerized plasmin fragment D; DM, diabetes mellitus; ED, Emergency Department; HLD, hyperlipidemia; HTN, hypertension; P/F, partial pressure of oxygen / fraction of inspired oxygen; qSOFA, quick Sequential Organ Failure Assessment; ROX, respiratory oxygenation; WBC, white blood cells.
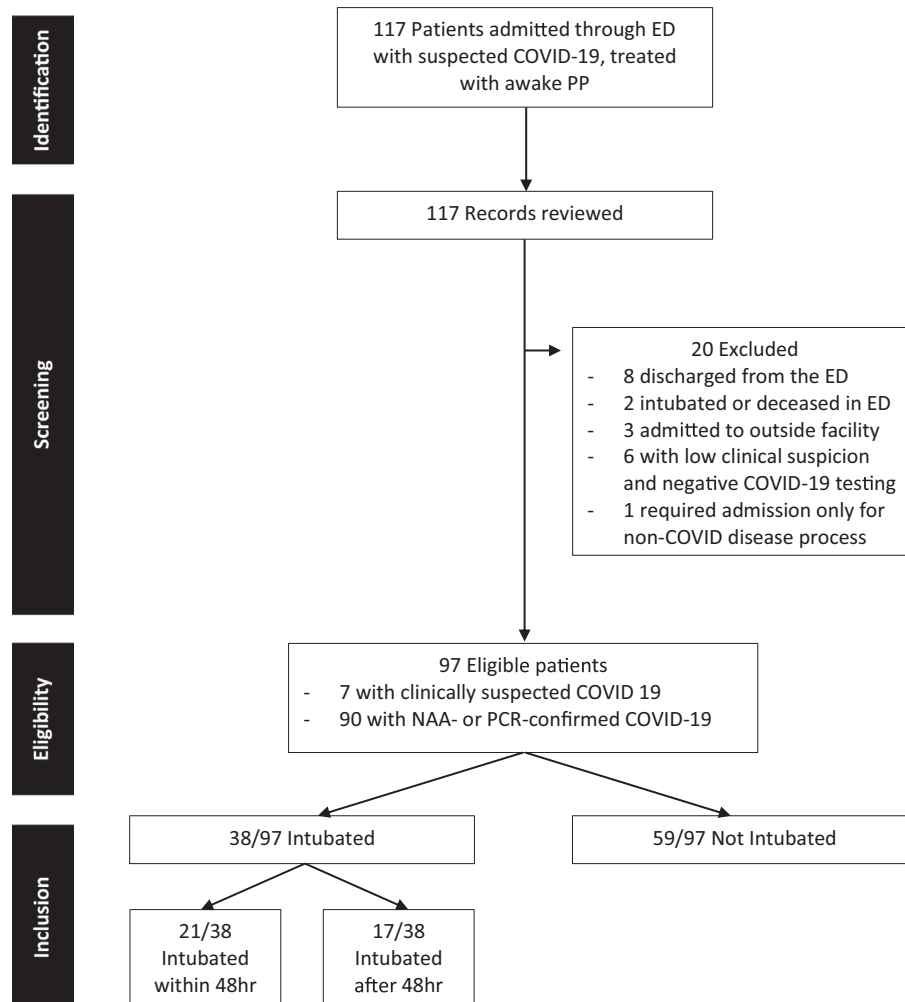
Appendix 3

Appendix A. Supplementary data

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Fig. C-2. Study flow diagram for patient selection.

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