Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Intubation rate of patients with hypoxia due to COVID-19 treated with awake proning: A meta-analysis

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ABSTRACT

Background: Awake prone positioning (PP), or proning, is used to avoid intubations in hypoxic patients with COVID-19, but because of the disease's novelty and constant evolution of treatment strategies, the efficacy of awake PP is unclear. We conducted a meta-analysis of the literature to assess the intubation rate among patients with COVID-19 requiring oxygen or noninvasive ventilatory support who underwent awake PP.
Methods: We searched PubMed, Embase, and Scopus databases through August 15, 2020 to identify relevant randomized control trials, observational studies, and case series. We performed random-effects meta-analyses for the primary outcome of intubation rate. We used moderator analysis and meta-regressions to assess sources of heterogeneity. We used the standard and modified Newcastle-Ottawa Scales (NOS) to assess studies' quality.
Results: Our search identified 1043 articles. We included 16 studies from the original search and 2 in-press as of October 2020 in our analysis. All were observational studies. Our analysis included 364 patients; mean age was 56.8 (SD 7.12) years, and 68% were men. The intubation rate was 28% (95% CI 20%–38%, $I^2 = 63\%$). The mortality rate among patients who underwent awake PP was 14% (95% CI 7.4%–24.4%). Potential sources of heterogeneity were study design and setting (practice and geographic).
Conclusions: Our study demonstrated an intubation rate of 28% among hypoxic patients with COVID-19 who underwent awake PP. Awake PP in COVID-19 is feasible and practical, and more rigorous research is needed to confirm this promising intervention.

1. Introduction

The development of acute respiratory distress syndrome (ARDS), or an ARDS-like syndrome, has been described among the majority of patients critically ill with COVID-19 and confers a high mortality rate, reported by some authors to surpass 90% [1-5]. The underlying pathophysiology of COVID-19 remains poorly understood. Using data from Seattle (Washington, USA) and Boston (Massachusetts, USA), researchers proposed that COVID-19 confers a type of "Pseudo-ARDS" characterized by diffuse atelectasis without the underlying alveolar and endothelial damage as observed in patients with traditional ARDS [2,6]. Patients with respiratory distress associated with COVID-19 respond quickly and well to positive pressure ventilation with apparent high recruitability [7]. The poor outcomes reported in many patients with COVID-19 that required early intubation, and the opportunity for clinical improvement suggested by high recruitability, have led many clinicians to investigate the implementation of recruitment methods to avoid mechanical ventilation.

Prone positioning (PP), or proning, is a well-established and commonly used treatment strategy for patients with severe ARDS: it has been shown to improve the P/F ratio—the ratio of partial pressure of oxygen (PaO2) to fraction of inspired oxygen (FiO2)—while reducing required positive end-expiratory pressure (PEEP), oxygen requirements, and ventilator-dependent days [8-11]. Additionally, when performed for more than 12 h per day, PP has been associated with a mortality benefit in severe ARDS patients requiring mechanical ventilation

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[8,9,12-15]. PP is thought to confer all of these benefits by decreasing transpulmonary pressure gradients and alleviating the compression of alveoli, thus reducing ventilator-induced lung injury [15-17]. In the supine position, ventral alveoli may be overinflated by mechanical ventilation (leading to volutrauma and barotrauma), while more dorsal alveoli are compressed (atelectrauma) by the ventral lung as well as the heart and diaphragm [17-22]. Proning is thought to even the distribution of gravitational forces and aeration within the lung and reduce the pressure exerted by the heart and diaphragm, reducing barotrauma, atelectrauma, and ventilation/perfusion mismatch [11,13,15,17,18,23]. Proning further promotes aeration of the posterior and basal lung fields by limiting the motion of the anterior chest wall [13,19,20], and has been associated with an improvement of secretion clearance [18,22]. PP may have greater effects when utilized in the earlier stages of ARDS development, when alveolar collapse is more likely to be reversible [16,20,24].

The current literature reports highly variable rates of intubation for patients with COVID-19 not undergoing awake PP, ranging from 55% to 88% [25-30]. The positive impact of proning on intubated patients with ARDS has led many to suggest applying this strategy to nonintubated awake patients [18,31,32]. Limited evidence collected to date of patients requiring respiratory support with supplemental oxygen, but not yet requiring mechanical ventilation, suggests that awake PP may improve oxygenation, prevent intubations, and improve patient outcomes [18,33]. However, the majority of the available evidence has been of relatively low quality, mostly in the form of case reports and small case series, due to COVID-19's novelty and the immediate need for data. In this systematic review and meta-analysis, we sought to evaluate the available evidence regarding the efficacy of awake PP and the prevalence of intubation in patients with COVID-19 undergoing awake PP.

2. Methods

2.1. Search selection and selection criteria

We conducted this study in accordance with the 2015 PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) statement [33]. We identified potentially eligible studies through a search of PubMed, Scopus, and Embase databases up through August 15, 2020. To include many potential studies, we used broad search terms: (covid-19 OR coronavirus OR sars-COV) AND (proning OR prone). Our study was not registered with the PROSPERO registry.

Given the dynamic development of data and the novelty of the disease state of interest, we included meeting and poster abstracts, case series, retrospective and prospective studies, and randomized and quasi-randomized trials in our analysis. To improve our study's quality, power, and timeliness, we also included eligible in-press articles that became available while we were preparing the manuscript. We included studies of adult patients (age > 18 years) who underwent PP while awake and alert, prior to intubation and invasive mechanical ventilation. Studies were eligible regardless of the level of noninvasive oxygen support required by their included patients (no oxygen, low-flow oxygen by nasal cannula, high-flow nasal cannula [HFNC], or bilevel or continuous positive airway pressure [BiPAP or CPAP]).

We contacted authors of studies that met all inclusion criteria but did not report the rate of invasive mechanical ventilation. We excluded studies that were not in the English language, included nonhuman subjects, did not present original data (that is, any commentaries or reviews), or were case reports (due to their publication bias and because they would not reflect the true rate of intubation among proned patients). Studies were also excluded if they included pediatric patients, failed to implement PP prior to intubation, or did not report intubation rates.

Our team emailed the corresponding authors of 7 studies to request additional information or clarification of reported data. Two authors responded, but only one provided additional data.

We used Covidence (www.covidence.org; accessed 9 December 2020) to manage the references for our meta-analysis. Two authors independently reviewed each title and abstract. A third author independently adjudicated any disagreements. Each title and abstract required 2 agreements to advance to full-text reviews. We used the same process for the full-text screening step.

2.2. Outcomes

Our primary outcome of interest was the rate of endotracheal intubation and invasive mechanical ventilation among patients with COVID-19 undergoing awake PP. Secondary outcomes were the rate of intubation within 24 h of presentation and any mortality rate as reported by the authors.

2.3. Quality assessment

Two authors evaluated each included study to determine study quality, with disagreements resolved through discussion between the 2 and a third author. We assessed the quality of observational cohort studies using the Newcastle-Ottawa Scale (NOS) [34] or the modified NOS [35] for case series. The NOS assesses each study according to 3 domains (selection of the cohort, comparability of the groups, and quality of outcome), and awards a maximum of 9 points. High-quality studies have a score ≥ 7, whereas moderate- and low-quality studies have scores of 4–6 and ≤ 3, respectively. The modified NOS assesses the same 3 domains but awards a maximum of 5 points because of case series' limitations. As a result, no case series can achieve higher than low to moderate quality.

Interrater agreement was assessed using weighted kappa scores, with a score of <0.2 corresponding to poor agreement; 0.21–0.4, fair agreement; 0.41–0.6, moderate agreement; 0.61–0.8, good agreement; and 0.81–1.00, very good agreement. We assessed heterogeneity by using both the Q statistic and the I^2 statistic. The Cochran Q statistic tests the null hypothesis that all studies in the analysis would share a common effect size, if the value of the Q statistic is less than or equal to the degree of freedom. The I^2 statistic provides the percentage of total variance as a difference in effect size across studies.

2.4. Data extraction

We extracted data into a standardized Excel spreadsheet (Microsoft Corp). We collected data regarding patient demographics (including age and comorbidities), initial vital signs, initial laboratory data (including blood gas analysis as well as inflammatory markers thought to be associated with severity of COVID-19 [36]), radiographic findings, noninvasive ventilation (NIV) type and settings, time to NIV and proning, total proning hours, improvement in P/F ratio after proning, and intubation and mortality rates.

To ensure adequate interrater agreement, at the start of the project, the 3 authors who performed all subsequent data extraction extracted data from the same 6 studies. The third of these authors then ran kappa scores to assess interrater reliability for consistency in our data extraction. After this initial test to ensure acceptable interrater reliability, 2 authors proceeded to extract data for each study. Any conflict was discussed and resolved as a group.

2.5. Statistical analysis

We selected a meta-analysis as our main inquiry into this clinical question due to the unique situation of the disease: the COVID-19 pandemic has spread across multiple very different regions of the world over the course of almost a year. The practice of awake PP has been

utilized in several different practice and geographic settings during this time as well. By performing a meta-analysis and subgroup analyses, we hoped to assess and compare outcomes associated with the disease and this particular intervention across different global regions and time periods. Due to the uncertainties of the disease and the process of awake PP, the performance of meta-regressions provided further ways to detect clinical factors associated with the outcome of interest, with the aim of providing clinicians with valuable information to guide clinical practice or future research.

We used random-effects models to measure the rate of outcomes across the pooled patient population. Any studies reporting 2 similar outcomes were eligible for random-effects meta-analysis. We expressed categorical variables as percentages and continuous variables as means. Since many authors did not report standard deviations for the means of their continuous variables, we did not report standard deviations in our results. For studies that reported medians and interquartile ranges, we converted median to mean and SD as previously described by Lou et al. [37]. We also performed subgroup analyses to identify potential sources of heterogeneity and possible differences between subgroups. We a priori defined categorical moderator variables, including study design, World Health Organization region according to the country of study, months of publication (as all included studies were published in 2020), type of oxygen delivery devices used, and the number of patients in each study. We performed histogram analysis of continuous variables before categorizing them into groups as needed, according to their frequency of distribution.

We used meta-regressions and continuous independent variables, as available from any study, to assess potential variables associated with endotracheal intubation and invasive mechanical ventilation. These continuous independent variables included age, percentage male, P/F ratio and respiratory rate oxygenation (ROX) index at triage, change in P/F ratio and ROX index between triage and earliest repeat, and number of days proning. For studies that did not report P/F ratio or ROX index, we calculated the values from the reported components. The ROX index is a clinical prediction rule that estimates the likelihood of intubation in patients requiring HFNC in the management of hypoxemic respiratory failure, calculated from respiratory rate, oxygen saturation, and FiO2. Risk of intubation is low if ROX index is ≥4.8 and high if ROX index is ≤3.8 [38]. The P/F ratio assesses lung function in acute lung injury. A P/F ratio less than 300 suggests mild ARDS, a value <200 is suggestive of moderate ARDS, and a value <100 represents severe ARDS [38].

We also performed sensitivity analysis by using "remove-one study" random-effects meta-analysis to assess the effect of each individual study on the overall effect size. We did not perform a funnel plot to assess publication bias in our study. Traditionally, a funnel plot is utilized to estimate whether the missing negative studies would change the interventions' overall effect size [39]. Our meta-analysis only measured the prevalence of intubation, so tests for publication bias were not applicable. We performed our meta-analysis using the software Comprehensive Meta-Analysis (www.meta-analysis.com; accessed 9 December 2020).

3. Results

3.1. Study selection

Our electronic search identified 1043 studies. After reviewing 56 full-text articles, we included 16 studies from our original search in our analysis. We also reviewed and added 2 in-press articles that became available in October 2020, after our initial search query (Fig. 1). Five (28%) of our studies were prospective, and 13 were retrospective. The majority of the selected studies were case series ($n = 13$, 72%), and the remaining were cohort studies (Table 1). Four studies included a control group, and 3 of these reported our outcome of interest.

The kappa score for data extraction was 0.9 (95% CI 0.6–0.99), which demonstrated "very good" interrater agreement.

3.2. Study quality

We assessed the quality of most studies included in our meta-analysis as low to moderate quality, with 4 studies (22%) graded as high quality (Table 1). The weighted kappa score for the study quality assessments was 0.62 (95% CI 0.4–0.83), which reflects good interrater agreement.

3.3. Summary of studies

Our meta-analysis included a total of 364 patients with COVID-19 who underwent awake PP during their hospitalization (Table 2). One hundred and seven patients (29%) underwent awake PP in the emergency department, 73 (20%) in a non-intensive care setting (step-down, intermediate care unit, or hospital wards), and 26 (7%) in an intensive care unit (ICU); 87 (24%) patients were reported as a mix of ICU and non-ICU patients. The clinical setting was not reported in 71 patients. Our patient population's mean age was 56.8 (SD 7.12), and 68% were men. The majority of the studies were from the European region (33%), followed by Region of the Americas and Western Pacific Region (28% each), and Eastern Mediterranean Region (11%).

Eight (44%) studies reported using a mixture of CPAP, HFNC, and low-flow nasal cannula for oxygen delivery and ventilatory support; 4 (22%) used CPAP; and 3 used HFNC. The remaining 3 studies did not report the type of oxygen delivery device used. Mean oxygen delivered was 50.8 l per minute and 70% FiO2 (SD 20.2).

Fifteen studies reported an initial (prior to awake PP) P/F ratio or the data needed to calculate it, and 12 studies reported repeat (after awake PP) values. Among these, the mean initial P/F ratio was 160.7 (SD 71.5) and mean repeat P/F ratio was 183.2 (SD 47.7). Eleven studies reported an initial (prior to awake PP) ROX index or its components, and 9 studies reported repeat (after awake PP) values. Among these, the mean initial ROX index was 8.8 (SD 3.7), and the mean repeat ROX index was 8.8 (SD 5.4).

3.4. Primary outcome: prevalence of intubation

Out of the 364 patients with COVID-19 who underwent awake PP, our analysis identified an intubation rate of 28% (95% CI 20%–38%) (Fig. 2). The Q statistic was 45 with 17 degrees of freedom, and the P value was 0.001, which suggested that the effect sizes were different from the true effect size across the studies in our meta-analysis. The I^2 statistic was 63%, which suggested that 63% of variance in the observed effects was due to variance in true effects and not to chance.

The prediction interval (Fig. 2) was between 8% and 64%, suggesting that 95% of comparable studies would report a rate of intubation from as low as 8% to as high as 64%. As a result, some future studies are expected to report a low intubation rate, while other studies would report a relatively high intubation rate.

3.4.1. Subgroup analysis

When studies were grouped by World Health Organization region, we found a higher percentage of intubation seen in the Americas and European regions, 33% and 31% respectively, and a lower percentage in the Western Pacific and Eastern Mediterranean regions, 22% and 13% respectively (Table 3A). However, the overall difference between these groups was not statistically significant. (See Table 3B.)

When studies were grouped according to study design, we observed similar rates of intubation per design, with prospective studies having less heterogeneity (Table 3A). Less heterogeneity was also seen in studies with fewer than 10 patients, and these studies also had lower intubation rates; but the overall difference among studies grouped by patient

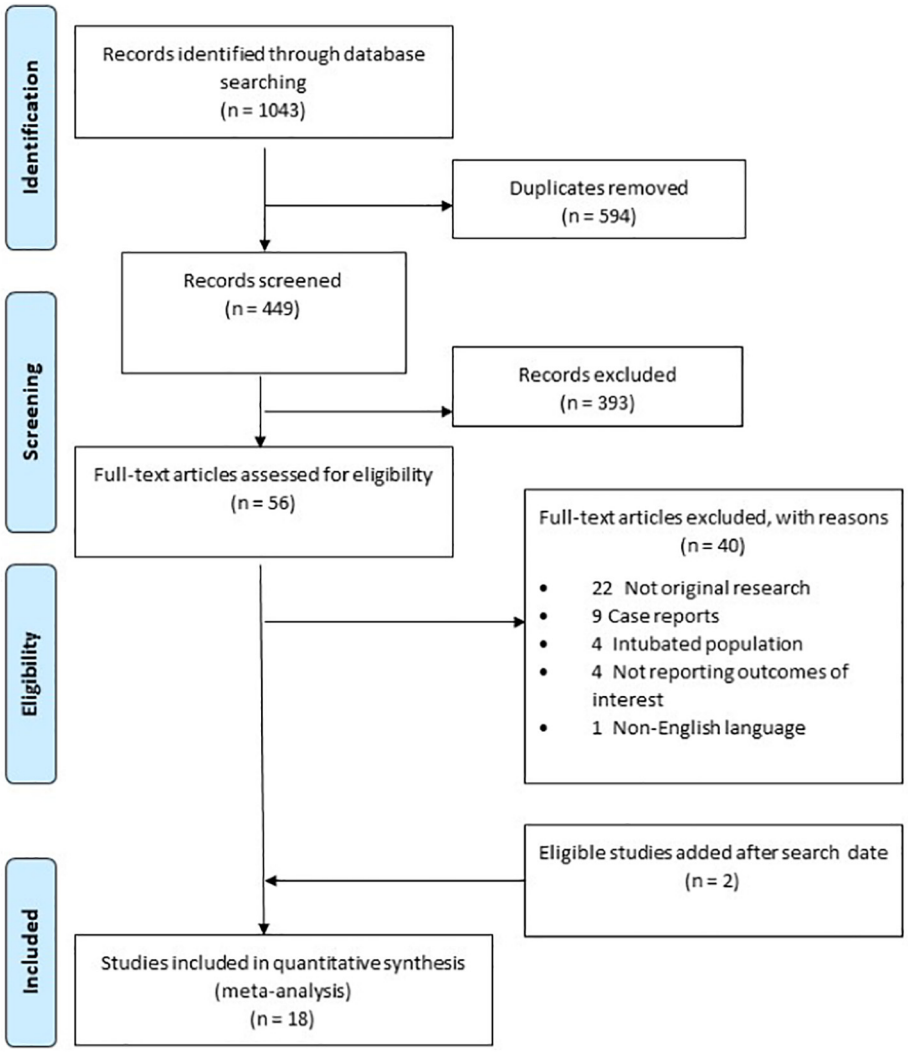

Fig. 1. PRISMA flow diagram for study selection.

Table 1
Characteristics of studies included in meta-analysis

First author	Month of publication	Country and WHO region of study	Study design	Study type	Clinical setting	Study quality grading*
Caputo [41]	May	USA; PAHO	Prospective	Cohort	ED	5
Cohen [42]	July	Israel; EMRO	Retrospective	Case series	Not reported	4
Coppo [43]	June	Italy; EURO	Prospective	Cohort	ED/ICU/non-ICU	6
Damarla [44]	June	USA; PAHO	Retrospective	Case series	ICU	5
Despres [45]	May	France; EURO	Retrospective	Case series	ICU	4
Elharrar [46]	May	France; EURO	Prospective	Case series	Not reported	5
Golestani-Eraghi [47]	May	Iran; EMRO	Retrospective	Case series	ICU	3
Huang [48]	June	Singapore; WRPO	Retrospective	Case series	Not reported	5
Jagan [25]	October	USA; PAHO	Prospective	Cohort	Non-ICU/ICU	7
Moghadam [49]	May	Iran; EMRO	Retrospective	Case series	Non-ICU	4
Ng [50]	July	Singapore; WRPO	Retrospective	Case series	Non-ICU	5
Padrão [26]	October	Brazil; PAHO	Retrospective	Cohort	ED	8
Ripoll-Gallardo [51]	July	Italy; EURO	Retrospective	Case series	Non-ICU	2
Sartini [52]	May	Italy; EURO	Retrospective	Case series	Non-ICU	5
Thompson [53]	June	USA; PAHO	Retrospective	Cohort	Non-ICU	8
Tu [54]	May	China; WRPO	Retrospective	Case series	Not reported	4
Xu [55]	May	China; WRPO	Retrospective	Case series	Not reported	5
Zang [27]	July	China; WRPO	Prospective	Case series	Not reported	8

Abbreviations: ED, emergency department; ICU, intensive care unit; PAHO, Pan American Health Organization; EURO, WHO European Region; WRPO, Regional Office for the Western Pacific; EMRO, Regional Office for the Eastern Mediterranean.
The Newcastle-Ottawa Scale (NOS) and modified NOS were used to assess the methodological quality of the included studies. High quality studies have a score ≥ 7, moderate and low quality studies have scores of 4–6 and ≤ 4 respectively*.

Table 2
Patient characteristics

First author	Number of proned patients	Mean age	Male n (%)	BMI	Initial P/F ratio	Initial ROX index	Oxygen delivery device (% patient use)	Daily proning duration, h	Total proning duration, h	Repeat PF ratio	Repeat ROX index	Intubation in 24 h	Any intubation	Total death
Caputo [41]	50	59	30 (60%)	NR	108	11	NC (24%), NRBM (76%)	NR	NR	197	NR	13	18	NR
Cohen [42]	2	46	1 (50%)	NR	252	15	NC (50%), HFNC (50%)	4	NR	145	4	0	0	0
Coppo [43]	47	57	44 (94%)	28	181	8	CPAP (79%)	3	21	193	6	NR	13	5
Damarla [44]	10	56	7 (70%)	NR	181	8	NC (50%), HFNC (40%)	4	NR	224	9	2	2	0
Despres [45]	6	59	6 (100%)	27	187	NR	NC (66%), HFNC (33%)	3	3	205	NR	NR	3	NR
Elharrar [46]	24	66	16 (67%)	NR	214	15	NC (67%), HFNC (33%)	NR	NR	246	15	NR	5	NR
Golestani-Eraghi [47]	10	NR	NR	NR	150	NR	CPAP (100%)	NR	9	NR	NR	NR	2	2
Huang [48]	3	59	2 (67%)	NR	102	8	HFNC (100%)	NR	32	139	8	NR	1	NR
Jagan [25]	40	56	8 (20%)	31	NR	NR	NR	NR	NR	NR	NR	NR	4	0
Moghadam [49]	10	41	7 (70%)	NR	NR	NR	NR	NR	NR	NR	NR	0	0	0
Ng [50]	10	60	8 (80%)	NR	310	NR	NC (60%), VM (20%), HFNC (10%)	5	25	NR	NR	NR	1	1
Padrão [26]	57	51	40 (70%)	33	196	9	NC (34%), VM (5%), NRBM (61%)	NR	NR	224	20	NR	33	6
Ripoll-Gallardo [51]	13	66	11 (84%)	NR	115	5	CPAP (100%)	NR	7	166	6	3	9	7
Sartini [52]	15	59	13 (86%)	24	157	6	CPAP (100%)	NR	NR	91	7	NR	1	1
Thompson [53]	25	67	18 (72%)	31	15	8	NR	4	8	NR	NR	NR	12	3
Tu [54]	9	51	4 (44%)	NR	86	NR	HFNC (100%)	2	10	135	NR	NR	2	NR
Xu [55]	10	50	5 (50%	NR	157	NR	HFNC (100%)	6	NR	233	NR	0	0	0
Zang [27]	23	63	13 (56%)	NR	NR	3.35	NC (68%), HFNC (22%)	8	3	NR	4	NR	8	10

Abbreviations: BMI, body mass index; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; NC, nasal cannula; NR, not reported; NRBM, non-rebreather mask; P/F, partial pressure of oxygen / fraction of inspired oxygen; ROX, respiratory rate oxygenation; VM, Venturi mask.

sample size was not statistically significant (this is likely reflecting "small study effect") (Table 3A).

The rate of intubation increased as the year 2020 progressed, with 24% in the months of April and May and 32% in the months of August to October (Table 3A); this difference was not statistically significant in subgroup analysis.

3.4.2. Sensitivity analysis

Our sensitivity analysis, using random-effects meta-analysis with one study removed, found the rate of any intubation 28% (95% CI 20%–38%), suggesting that our results are robust and not disproportionately affected by any single study.

3.5. Secondary outcomes

3.5.1. Intubation within 24 hours of presentation

Six studies reported the number of patients with COVID-19 who underwent awake PP and were intubated within 24 h of presentation (Fig. 3A). These studies report a total of 29 patients intubated during hospitalization, 18 (62%) of whom were intubated within 24 h of presentation, with an overall 24-h intubation rate of 22% (95% CI 14.7%–32.2%). The *Q* statistic was 3.5 with 5 degrees of freedom, and the *P* value was 0.61, which suggested that this effect size was similar across the studies in our meta-analysis. The I^2 statistic was 0%, suggesting low heterogeneity of effect size across the studies.

3.5.2. Mortality

The pooled mortality rate for the 13 studies that reported death rates was 14% (95% CI 7.4%–24.4%) (Fig. 3B). The *Q* statistic was 32 with 12 degrees of freedom, and the *P* value was 0.001, which suggested the true effect size was different across the studies in our meta-analysis. The I^2 statistic was 62%, which suggested that 62% of variance in the observed effects was due to variance in true effect sizes.

4. Discussion

Our meta-analysis investigated the need for invasive mechanical ventilation among patients with COVID-19 and hypoxia managed with awake PP in addition to supplemental oxygen or NIV and demonstrated an intubation rate of 28%, though with a wide prediction interval. The reported rates of intubation among patients with COVID-19 who have not undergone awake-PP have been highly variable (as has been the case with patients treated with awake-PP), ranging from 5% to 88% [25-30]. However, most of the rates reported among hypoxic patients with COVID-19 requiring supplemental oxygen or NIV (whose acuity more closely matches those who demonstrate a need for awake-PP) have been equal or higher than that identified in our study, but overall ranging from 11% to 88% [25-30]. Three of the studies included in this meta-analysis (Jagan, Padrão, and Zang) included a control group and reported intubation rates of 28% (unadjusted), 49%, and 11%, respectively [25-27]. Of note, although the rate of intubation reported by Zang et al. was lower (11%) in the non PP group than in the PP group (35%), patients

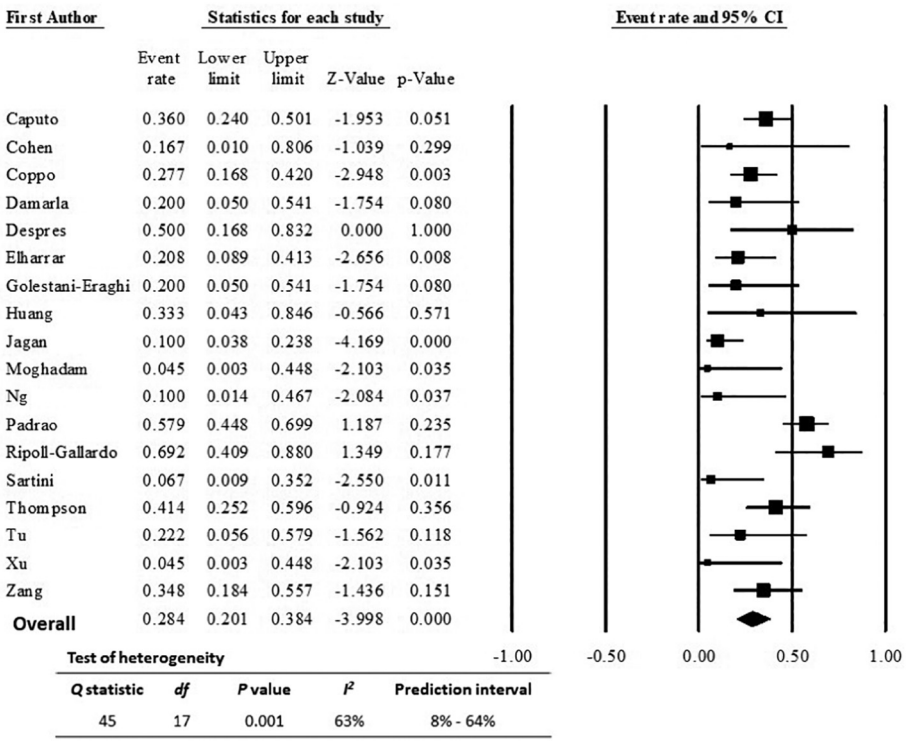

Fig. 2. Forest plot of random-effects meta-analysis for prevalence of any intubation during hospitalization among patients with COVID-19 undergoing awake proning.

who did not undergo PP, had a statistically significant longer length of stay (27 days compared to 8 days, p-value <0.01) and higher mortality rate (75.7% in comparison to 43.5%, p-value = 0.01) than those who did undergo awake PP.

The majority of the studies included in our meta-analysis are single-center, and it is thus difficult to generalize their results outside the specific setting in which they were performed. By integrating their results, our meta-analysis provides insight into the expected results from a multi-center study. The heterogeneity of studies included in this analysis was high. One reason for this heterogeneity may be explained by our inclusion of studies from a variety of practice settings (emergency departments, general wards, and ICUs) as well as different countries with potentially variable practice patterns, health care resources, and types of therapeutic treatment. However, our overall outcome did not change significantly when any single study was removed from the analysis, suggesting that our results, while not precise, are robust and broadly applicable to a wide range of clinical settings.

Similar intubation rates were observed in both prospective and retrospective studies, though less heterogeneity was observed among prospective studies, as researchers might have had more control of the data collection and patient selection. Similarly, smaller studies—particularly case series—generally reported lower intubation rates (though the difference in rates was not statistically significant) and were associated with less heterogeneity, implying the "small study effect," in which

Table 3A
Results from moderator analyses using categorical variables and outcome of any intubation during hospital stay

Moderator variables		Number of studies	Any intubation (%)	95% CI	Q statistic	*df*	*P* value	I^2	Between group comparison *P* value
WHO region									**0.55**
	EMRO	**2**	**13**	**3%–47%**	**1**	**1**	**0.32**	**1%**	
	EURO	**6**	**31**	**17%–51%**	**13**	**5**	**0.024**	**61%**	
	PAHO	**5**	**33**	**19%–51%**	**21**	**4**	**0.001**	**80%**	
	WPRO	**5**	**22**	**9%–43%**	**4**	**4**	**0.39**	**4%**	
Study design									**0.81**
	Prospective	**4**	**30**	**16%–49%**	**2**	**3**	**0.55**	**0**	
	Retrospective	**14**	**27**	**17%–40%**	**42**	**13**	**0.001**	**69%**	
Patient sample size									**0.36**
	≤ 10 patients	**9**	**19**	**10%–35%**	**6**	**8**	**0.59**	**0**	
	11–39 patients	**5**	**34**	**19%–54%**	**12**	**4**	**0.02**	**67%**	
	≥ 40 patients	**4**	**32**	**18%–51%**	**22**	**3**	**0.001**	**86%**	
Month of publication									**0.84**
	April–May 2020	**7**	**24**	**11%–43%**	**7**	**6**	**0.28**	**20%**	
	June–July 2020	**9**	**29**	**17%–45%**	**16**	**8**	**0.049**	**48%**	
	August–October 2020	**2**	**32**	**12%–61%**	**18**	**1**	**0.001**	**94%**	
Types of oxygen delivery device									**0.63**
	CPAP	**4**	**33**	**13%–61%**	**10**	**2**	**0.006**	**80%**	
	HFNC	**3**	**19**	**5%–49%**	**2**	**2**	**0.44**	**0**	
	Mixed	**8**	**33**	**21%–46%**	**19**	**8**	**0.015**	**58%**	

Table 3B
Results from meta-regression measuring the associations between continuous variables and outcome of any intubation during hospital stay

Moderator variables	Number of studies	Correlation coefficient	95% CI	*P* value	R^2	I^2
Age - years	**17**	**0.06**	**−0.02, 0.14**	**0.14**	**0**	**66%**
Percent of male patients	**17**	**1.7**	**−1.3, 5.01**	**0.3**	**0**	**65%**
BMI	**6**	**0.15**	**−0.13, 0.43**	**0.29**	**0.1**	**81%**
Initial P/F ratio[a]	**12**	**0**	**−0.01, −0.85**	**0.4**	**0**	**66%**
Delta P/F ratio[a]	**12**	**0.01**	**−0.01, 0.03**	**0.36**		
Initial ROX index[b]		**−0.07**			**0.51**	**67%**
	11		**−0.2, 0.08**	**0.45**		
Delta ROX index[b]	**9**	**0.1**	**−0.01, 0.2**	**0.06**		
Proning duration per day (hours)	**8**	**0.04**	**−0.19, 0.26**	**0.76**	**0**	**1%**
Total duration of proning (hours)	**9**	**−0.04**	**−0.09, 0.01**	**0.12**	**0.47**	**31%**

[a,b]Multivariable meta-regressions included both continuous variables.
95% CI, 95% confidence interval; BMI, body mass index; Delta, change between initial and repeat values of ROX index or P/F ratio; P/F ratio, PaO2 (partial pressure of oxygen)/FiO2 (fraction of inspired oxygen) ratio; ROX index, respiratory oxygen index.

small studies with favorable results were more preferentially reported and published [56].

Given the significant flux, rapid evolution, and uncertainty of treatment strategies for COVID-19, high heterogeneity in published studies is to be expected. We observed that our meta-analysis' heterogeneity was lower than that of other meta-analyses reporting prevalence of disease related to COVID-19 [57,58]. Over the time period covered by the studies included in our analysis, popular and recommended treatment

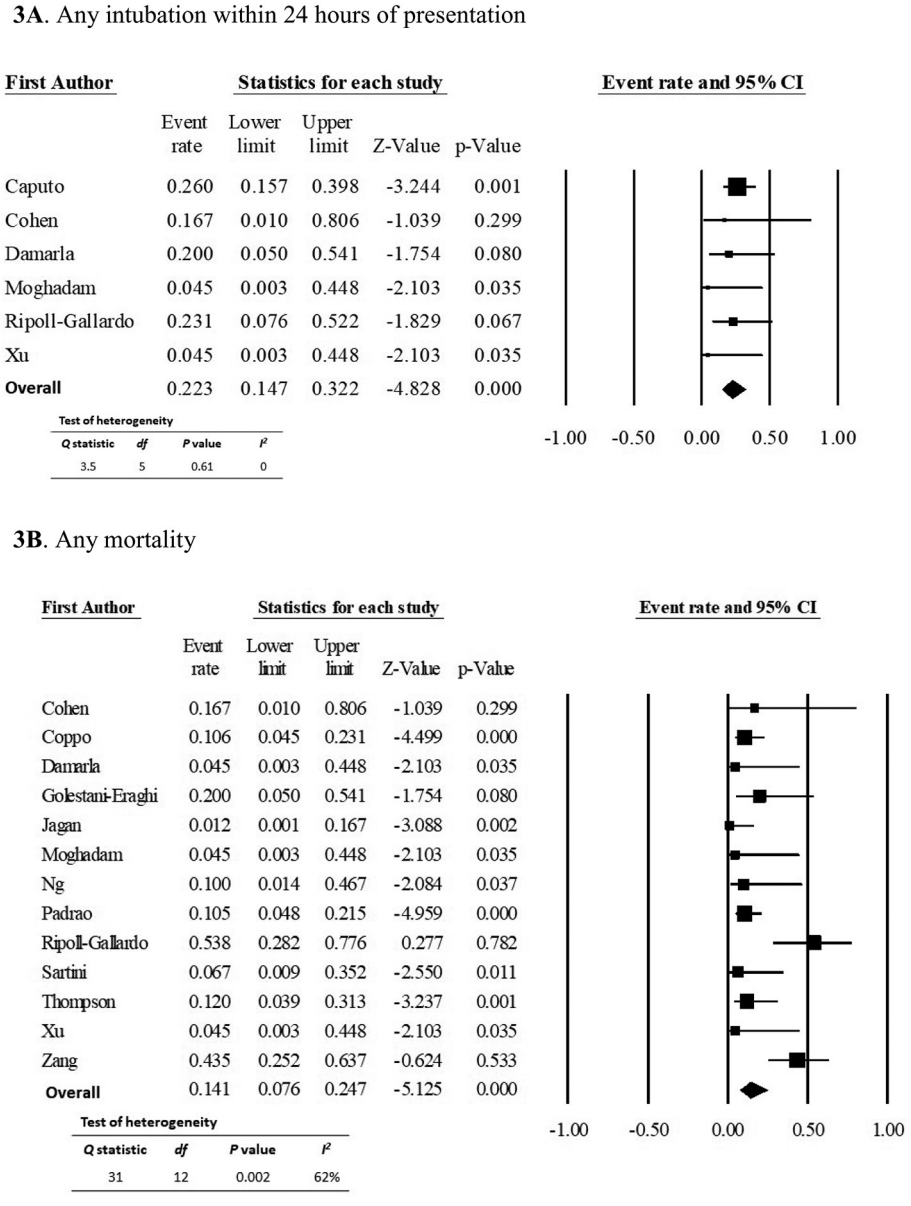

Fig. 3. Forest plot of secondary outcomes for COVID-19 patients undergoing awake proning **3A**. Any intubation within 24 h of presentation **3B**. Any mortality.

strategies have changed significantly, from the initial excitement and subsequent debunking of hydroxychloroquine and the confounding recommendations surrounding remdesivir [59], to the data supporting the early use of dexamethasone [60]. Our meta-analysis highlights the inherent difficulty in seeking precise results in a novel and continually shifting environment. However, our meta-analysis suggested that the prevalence of intubation was consistent across clinical settings and different regions and through the uncertainty of therapeutic treatments. As a result, awake PP may be a promising intervention until results from further studies become available.

Our results further highlight the nuances involved in the clinical decision to intubate and the difficulty in capturing and reporting those nuances with objective measures. Specifically, P/F ratio and ROX index were not significantly associated with intubation rates in our multivariable meta-regressions. However, our exploratory results should not be taken to imply that either P/F ratio or the ROX index are not useful tools for assessing need for intubation among patients with COVID-19. There are a number of factors that can help explain these findings. We may not have enough studies within the meta-analysis to detect a significant association between intubation and P/F ratio or ROX index. Additionally, P/F ratio and ROX index are not the sole indicators of need for intubation in clinical practice. Most studies in our meta-analysis did not report additional important clinical factors regarding the decision to intubate, such as hemodynamic parameters, patients' mental status and work of breathing, signs of poor perfusion, and overall clinical picture. As such, our meta-regression may not show significant associations between P/F ratio or ROX index and intubation, without taking into account other clinical variables.

4.1. Implications for future research

Our analysis suggests that awake PP is practical and feasible in various practice settings and across the globe. It highlights the need for multicenter studies with adequate sample size, proper control groups, and more comprehensive reporting of additional therapeutic treatments. Such studies will have the potential to further elucidate not only the clinical predictors, but also the utility, of awake PP. These well-designed studies would help clinicians to differentiate which patients might benefit most from early versus later intubation, and who might avoid intubation altogether through proning and NIV. Additionally, the complications reported by the studies included in our meta-analysis are relatively minor, mostly related to patient discomfort or increased cough. Therefore, our study suggests that the risks associated with awake PP are low, and the potential benefits are substantial enough to warrant more rigorous investigation.

4.2. Limitations

Our analysis has many important limitations. Most of the included studies were of low to moderate quality, with no randomized trials and few including control groups. In addition, owing to the novelty of COVID-19 and the early push for data on treatment options and patient outcomes, as well as the prolonged hospitalizations required by some patients, many studies reported outcomes over a predefined time period, rather than a patient's entire hospital course. This limits our understanding of the impact of awake PP on the patient's full disease course.

Furthermore, many included studies did not report data on key indicators of patients' respiratory status, such as P/F ratios, ROX index, or chest X-ray or computed tomography (CT) results, which prevents full and accurate characterization of the patient population included. This in turn limits our ability to identify patients most or least likely to benefit from awake PP.

Overall, this meta-analysis has served primarily as an exploration of available data and to highlight the need for more rigorous studies in the future. Because of the low quality of the studies available at this time, we agreed with the recommendations from the National Institute of Health's expert panel that awake PP may be trialed for hypoxic patients, but it should not be relied on as a rescue therapy to avoid intubation altogether [61].

5. Conclusion

Awake PP is a practical and promising intervention for patients requiring supplemental oxygen or NIV due to COVID-19 and may serve to prevent intubations. The intubation rate among such patients is estimated at approximately 30%. More rigorous studies are needed to confirm this observation and further elucidate which patients might benefit most from awake proning to avoid intubation.

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Authors' contributions

Conceptualization: QKT, BS, DM, JD, SC, RA.
Data collection: RA, SC, JD, MR, VB, IY, FY, BS, DM, QKT.
Data quality and data analysis: RA, SC, JD, MR, VB, IY, FY, QKT.
Manuscript preparation: RA, SC, JD, QKT.
Critical revision of manuscript: RA, SC, JD, MR, VB, IY, FY, BS, DM, QKT.
Abbreviation: PRISMA, preferred reporting items for systematic reviews and meta-analyses.
Adapted from [40].

Declaration of Competing Interest

The authors declare no conflict of interest.

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