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The POSITIONED Study: Prone Positioning in Nonventilated Coronavirus Disease 2019 Patients—A Retrospective Analysis

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Objectives: Given perceived similarities between coronavirus disease 2019 pneumonia and the acute respiratory distress syndrome, we explored whether awake self-proning improved outcomes in coronavirus disease 2019-infected patients treated in a rural medical center with limited resources during a significant local coronavirus disease 2019 outbreak.

Design: Retrospective analysis of prospectively collected clinical data.

Setting: Single-center rural community-based medical center in Grand Island, NE.

Patients: One hundred five nonintubated, coronavirus disease-infected patients.

Interventions: None.

Measurements and Main Results: After patients were educated on the benefits of awake self-proning, compliance was voluntary. The primary outcome was need for intubation during the hospital stay; secondary outcomes included serial peripheral capillary oxygen saturation measured by pulse oximetry to the Fio_2 ratios, in-hospital mortality, and discharge disposition. Of 105 nonintubated, coronavirus disease-infected patients, 40 tolerated awake self-proning. Patients who were able to prone were younger and had lower disease severity. The risk of intubation was lower in proned patients after adjusting for disease severity using Sequential Organ Failure Assessment scores (adjusted hazard ratio, 0.30; 95% CI, 0.09–0.96; $p = 0.043$) or Acute Physiology and Chronic Health Evaluation II scores (adjusted hazard ratio, 0.30; 95% CI, 0.10–0.91; $p = 0.034$). No prone patient died compared with 24.6% of patients who were not prone ($p < 0.001$; number needed to treat = 5; 95% CI, 3–8). The probability of being discharged alive and peripheral capillary oxygen saturation measured by pulse oximetry to the Fio_2 ratios were statistically similar for both groups.

Conclusions: Awake self-proning was associated with lower mortality and intubation rates in coronavirus disease 2019-infected patients. Prone positioning appears to be a safe and inexpensive strategy to improve outcomes and spare limited resources. Prospective efforts are needed to better delineate the effect of awake proning on oxygenation and to improve patients' ability to tolerate this intervention.

Key Words: acute respiratory distress syndrome; coronavirus disease 2019; hypoxia; prognosis; prone

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Severe acute respiratory syndrome coronavirus 2, the novel coronavirus responsible for the coronavirus disease 2019 (COVID-19) pandemic, has put an unprecedented strain on the healthcare system worldwide while causing significant morbidity and mortality (1). Viral pneumonia is the most frequent cause of hospitalization and hypoxemic respiratory failure is a common cause of ICU admissions (2). Because many COVID-19–infected patients have profound desaturations (blood oxygen saturations < 80%) but only modest symptoms, the term "happy hypoxemics" has evolved to describe individuals with this disconnect between their physiology and symptoms (3, 4). Roughly, 5% of COVID-19–infected patients require intubation and mechanical ventilation for respiratory failure caused by a viral pneumonia with clinical features that parallel the acute respiratory distress syndrome (ARDS) (5). Conventional ARDS, characterized by diffuse alveolar infiltrates, noncompliant lungs, and increased dead space ventilation, is associated with profound hypoxemia, significant morbidity, and substantial mortality. Although COVID-19 pneumonia is distinct from ARDS in that imaging often shows patchy infiltrates, lung compliance is relatively preserved, and dead space volume is relatively unchanged from normal, COVID-19 mirrors ARDS with profound hypoxemia, significant morbidity, and an alarming mortality rate (1, 2).

Randomized trials in conventional ARDS have shown that providing mechanical ventilation in the prone position improves the ratio of Pao_2 to Fio_2 (P/F) and reduces mortality (6–9). Given the perceived similarities between COVID-19 pneumonia and ARDS—coupled with a limited mechanical ventilation supply and concerns for iatrogenic infection during intubation—several groups explored the utility of prone positioning in nonventilated COVID-19 patients, so called "awake proning." These small studies have described improved P/F ratios with awake proning of COVID-19 pneumonia patients (10–12). At the time of submitting this article, there are no approved COVID-19–specific therapies and supportive care remains the mainstay of treatment (9, 13).

An unpleasant truth exposed by the COVID-19 pandemic is that a rapidly spreading respiratory virus can quickly overwhelm healthcare systems worldwide (14, 15). Because survivors of COVID-19–associated respiratory failure average 11 days on the ventilator and 17 days in the hospital, resource consumption is immense and shortages of mechanical ventilators, common ICU medications, and personal protective equipment are commonplace (16–18). Anecdotally, rural medical centers serving COVID-19 "hot spots" disproportionately struggle with these issues as their proportion of ICU beds are typically lower, fewer ventilators are available, and intensivist coverage is often limited. Further, transfer capabilities are hindered during surges by the sheer volume of requests for transfer and reluctance of Emergency Medical Services personnel to transport COVID-19 patients' long distances for a host of reasons.

Given reported improvements in the P/F ratio with awake proning in nonintubated COVID-19 patients, this strategy is an appealing strategy to conserve mechanical ventilators in resource-limited rural hospitals. Accordingly, we retrospectively explored whether awake proning decreased the rates of intubation in COVID-19–infected patients with hypoxic respiratory failure being treated in a rural Nebraska medical center overwhelmed by a large-scale local outbreak. We also assessed ability to tolerate awake proning and the effects on oxygenation in this unique real-world setting.

MATERIALS AND METHODS

Study Design and Patients

This retrospective study was considered exempt research by the Institutional Review Board at Creighton University (InfoEd Global record number: 2001116-01). We identified all admissions for COVID-19 between March 24, 2020, and May 5, 2020, to CHI Health St. Francis in Grand Island, Nebraska, a rural hospital with 16 ICU beds. All nonpregnant, COVID-19–infected patients greater than or equal to 19 years old (the age of majority in Nebraska) were reviewed. Of 126 eligible admissions identified, 21 were excluded for intubation at the time of admission (n = 12), repeat admission (n = 5), or incomplete records (n = 4), resulting in a final cohort of 105 unique patients.

Definition of Prone Status

All nonintubated COVID-19 patients were educated on the benefits of awake proning and were instructed to self-prone intermittently during the day and overnight. Patients were included for analysis in the prone group if there was nurse or physician documentation of self-proning for greater than or equal to one continuous hour on greater than or equal to five occasions per day and for greater than or equal to one continuous hour overnight. Patients in the supine group included those who did not meet these minimum frequencies and/or durations, those unable to tolerate the prone position, and those who refused. Patients, nursing staff, and respiratory therapists were instructed to inform the investigating physician if adverse events (falls, displacement of oxygen cannulas, pressure ulcers, etc.) were encountered because of proning.

Outcomes and Covariates

The primary outcome was need for intubation during the patient's hospital stay. Secondary outcomes included mortality, time to intubation, and changes in oxygenation as quantified by the peripheral capillary oxygen saturation measured by pulse oximetry to the Fio_2 (S/F) ratio. The noninvasive S/F ratio was used as a surrogate for the P/F ratio as the two are reliably correlated in various critical illnesses including ARDS (19–21). S/F ratios were abstracted every 4 hours for the first 48 hours from the time the patient was admitted to the hospital. If patients were intubated in the first 48 hours, S/F values were collected with censoring at the time of intubation. Covariates of interest included as follows: patient demographics (age, biological sex, body mass index, race/ethnicity, primary language, smoking status), severity of illness scores (Sequential Organ Failure Assessment [SOFA] and Acute Physiology and Chronic Health Evaluation [APACHE] II), comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, chronic hemodialysis, asthma, heart failure, coronary artery disease, rheumatoid arthritis, cancer, and immunocompromising disease), need for ICU admission, ICU length of stay (LOS), hospital LOS, and discharge disposition.

Statistical Analysis

Demographic and clinical characteristics were stratified by whether the patient met proning criteria or not. Depending on data distribution, continuous variables are presented as mean and SD or median and interquartile range, compared using independent samples t test or Mann-Whitney U test, respectively. Categorical variables are presented as percent, compared using the chi-square test or Fisher exact test. Rate comparisons are presented alongside number needed to treat (NNT) and Agresti-Coull CIs, as appropriate. Time-to-intubation during the hospital stay was compared using Kaplan-Meier method, whereas risk of intubation was compared using univariable and multivariable Cox proportional-hazards models. In both analyses, the patient was censored at in-hospital death, discharge from the hospital, or hospital day 28. Multivariable models included disease severity scores, which were estimated separately for SOFA and APACHE II scores given they are highly correlated but are calculated using different clinical variables. Hospital LOS was modeled as probability of being discharged alive via Kaplan-Meier analysis and Cox proportional-hazards models in which patients were censored at in-hospital death or on July 9, 2020 (the last day of data collection). The proportionality of hazards assumption was evaluated using Schoenfeld residuals for continuous variables and log-negative-log survival curves for categorical variables. Finally, differences across S/F ratio measurements were estimated using linear mixed-effects model to account for the correlation of observations from the same patient; two-way interactions were estimated to determine whether the effect of prone status differed across time or by baseline S/F ratio. For all models, the effects of continuous variables were estimated using restricted cubic splines with knot points at the 5th, 35th, 65th, and 95th percentiles (22). All statistical analyses were conducted using SAS v. 9.4 (SAS Institute, Cary, NC) with p value of less than 0.05 used to indicate statistical significance.

TABLE 1. Demographic Characteristics Stratified by Prone Status

Variable	Prone		p
	No (n = 65)	Yes (n = 40)	
Age	65.8 ± 16.3	56.0 ± 14.4	0.002
Biological sex			
Female	43.1	50.0	0.489
Male	56.9	50.0	
Body mass index	28.0 (24.9–34.4)	31.3 (26.4–37.5)	0.079
Underweight	1.7	2.5	0.159
Normal weight	25.0	10.0	
Overweight	33.3	27.5	
Obese	40.0	60.0	
Race/ethnicity			
White	54.74	37.8	0.106
Hispanic	42.2	62.2	
Other	3.1	0.0	
Primary language			
English	59.4	59.5	1.000
Spanish	39.1	40.5	
Other	1.6	0.0	
Smoking status			
Never	61.5	77.5	0.056
Current	1.5	5.0	
Former	36.9	17.5	
Vape	1.5	0.0	1.000

Data presented as mean ± SD, median (interquartile range), or percent.

RESULTS

Of the 105 patients, 40 (38.1%) were able to prone during the study period. Baseline demographic and clinical characteristics stratified by prone status are presented in **Tables 1** and **2**. Overall, patients who were prone were younger with lower disease severity as indicated by both SOFA and APACHE II, and lower rates of heart failure and immunocompromising disease.

None of the patients who were able to prone died during their hospital stay compared with 24.6% of patients who did not prone ($p < 0.001$; NNT = 5; 95% CI, 3–8). The unadjusted intubation rate was lower in patients who were prone (10.0% vs 27.7%; $p = 0.031$; NNT = 6; 95% CI, 4–30) and time-to-intubation was longer in patients who were prone (log-rank $p = 0.023$; **Fig. 1**). Unadjusted risk of intubation was 69% lower in patients who were prone (hazard ratio [HR], 0.31; 95% CI, 0.10–0.90; $p = 0.032$), an association

TABLE 2. Clinical Characteristics Stratified by Prone Status

Variable	Prone		p
	No (n = 65)	Yes (n = 40)	
ICU admission	40.4	27.3	0.212
Discharge disposition			
Home	41.5	72.5	< 0.001
Died	24.6	0.0	
Nursing home	9.2	5.0	
Still in hospital	10.8	15.0	
Other	13.8	7.5	
Severity scores			
Sequential Organ Failure Assessment	4 (2–5)	2 (2–3)	< 0.001
Acute Physiology and Chronic Health Evaluation II	10 (7–16)	7 (4–9)	0.008
Comorbidities			
Hypertension	55.4	60.0	0.643
Diabetes	38.5	45.0	0.508
Chronic obstructive pulmonary disease	16.9	12.5	0.540
Chronic kidney disease/end stage renal disease	23.1	12.5	0.180
Dialysis	8.6	0.0	0.153
Asthma	0.0	5.0	0.143
Heart failure	21.5	5.0	0.026
Coronary artery disease	16.9	7.5	0.240
Rheumatoid arthritis	3.1	0.0	0.524
Cancer	9.2	7.5	1.000
Immunocompromising disease	10.8	0.0	0.042

Data presented as median (interquartile range) or percent.

that remained constant after adjusting for SOFA scores (adjusted HR [aHR], 0.30; 95% CI, 0.09–0.96; $p = 0.043$) or APACHE II score (aHR, 0.30; 95% CI, 0.10–0.91; $p = 0.034$); **Figure S1** (http://links.lww.com/CCX/A367) for effect of SOFA score and APACHE II score. Although baseline differences were indicated for heart failure and immunocompromising disease, neither could be included in the multivariable model as there were not enough intubation events in patients with heart failure (intubation rate was 0.0% in patients who were prone compared with 21.4% in patients who were not prone; $p = 1.000$), whereas all immunocompromised patients were not prone (intubation rate: 28.6%) which precluded statistical comparison.

Median time-to-hospital discharge was lower in patients who were prone compared with patients who were not (9 d; 95% CI, 6–14 vs 14 d; 95% CI, 10–20 d; $p = 0.031$; **Fig. 2**). Further, patients who were prone were 57% more likely to be discharged alive compared with patients who were not (HR, 1.57; 95% CI, 1.02–2.42; $p = 0.039$); however, this difference became nonstatistically significant after adjusting disease severity using SOFA scores (aHR, 0.85; 95% CI, 0.47–1.53; $p = 0.587$) or APACHE II scores (aHR, 0.96; 95% CI, 0.56–1.66; $p = 0.893$); **Figure S2** (http://links.lww.com/CCX/A367) for effect of SOFA score and APACHE II score.

Finally, after adjusting for measurement timing and baseline S/F ratio, patients who were prone averaged 9.4-point lower S/F ratios compared with patients who were not prone (95% CI, 29.6 lower to 10.8 higher; $p = 0.360$), which was consistent across time and by S/F ratio at admission (interaction $p = 0.218$ and 0.056, respectively; **Fig. 3**). Overall, S/F ratios decreased through the first 24 hours of admission and remained consistently higher in patients who had higher S/F ratios at admission (both $p < 0.001$).

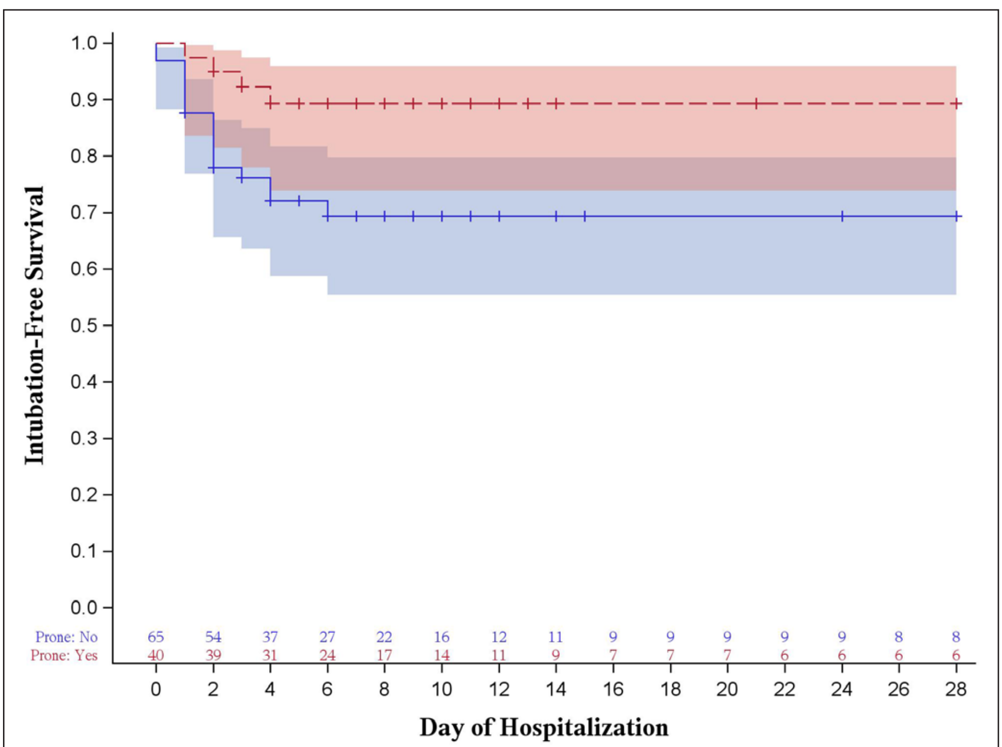

Figure 1. Time-to-intubation stratified by prone status (log-rank $p = 0.023$). *Shaded areas* represent 95% CIs.

DISCUSSION

Although rural hospitals provide healthcare to many Americans, these facilities have limited resources—both manpower and financial—and are rarely the focus of clinical research investigations (23). The current pandemic highlights the disparities of living in relatively remote areas as patients in rural communities are older, have more comorbidities, and are less likely to be tested for COVID-19 than patients in urban areas (24). Similar discrepancies in healthcare access and delivery exist between developed countries and developing countries around the world.

Accordingly, we conducted this retrospective study using data from a rural hospital overwhelmed by an unexpected surge in COVID-19 caused by a large-scale local outbreak to assess whether awake proning—a free and patient-driven endeavor—could reduce the need for an extremely limited supply of mechanical ventilators. In this resource-limited setting, we found that awake self-proning: 1) was surprisingly well tolerated with documented compliance in 38% of patients; 2) decreased the risk for intubation by 69%; and 3) reduced mortality with a NNT of five. Although older and sicker patients were less likely to successfully prone, these findings were consistent after adjusting analyses for age and severity of illness. Awake proning effectively allowed triage of ventilators to patients presenting with more severe COVID-related respiratory failure and to patients requiring mechanical ventilation for non-COVID etiologies (25). Unlike mechanical ventilation, and consistent with another smaller study in COVID-19–infected patients, awake self-proning was not associated with any adverse effects or treatment-related complications (26, 27).

In conventional ARDS, the mechanisms whereby prone positioning improves oxygenation are complex. Prone positioning improves gas exchange through decreased transpulmonary pressure (the difference between airway opening pressure and pleural pressure). With prone positioning, the weight of intrathoracic and abdominal viscera is unloaded from the lungs and restricted diaphragmatic excursion is relieved. Additionally, proning increases aeration of poorly ventilated alveolar units as dorsal portions of lung that are rich in gravity-dependent blood flow are placed in a nondependent position (8). The net benefits of proning in ARDS include a more homogenous distribution of aeration, improved ventilation-perfusion matching, increased secretion clearance, and lung protection and reduced mortality (6).

While all of these benefits would be anticipated with awake proning of COVID-19 patients—and one previous study showed improved oxygenation with awake prone positioning in COVID-19—we did not

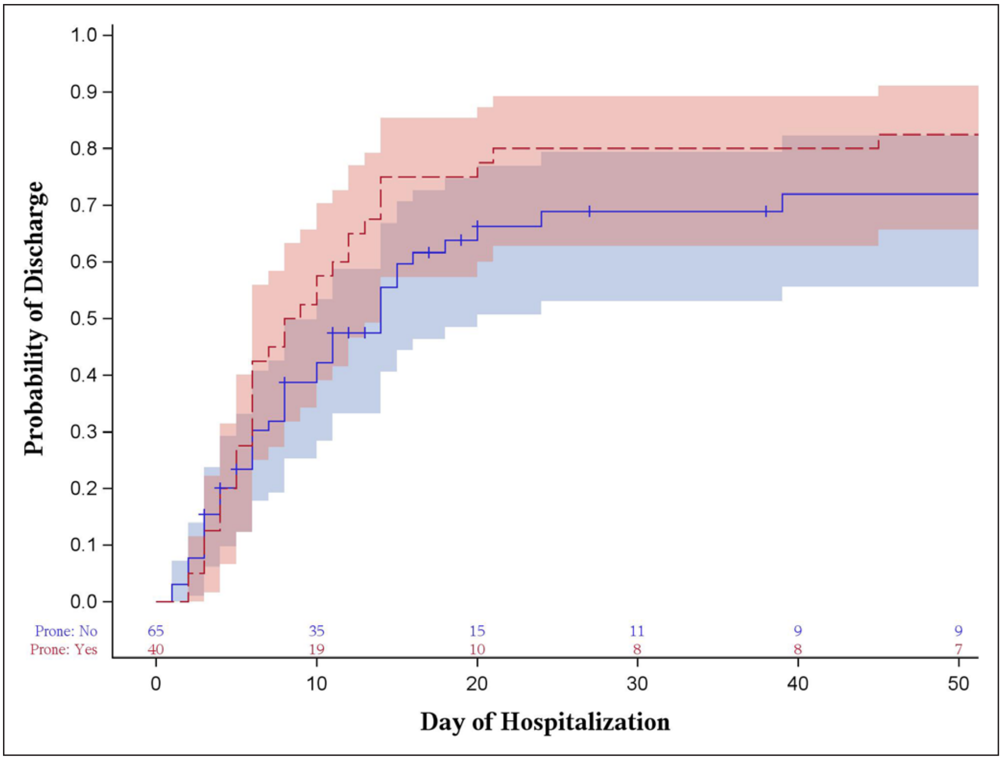

Figure 2. Probability of hospital discharge stratified by prone status (log-rank $p = 0.031$). *Shaded areas* represent 95% CIs.

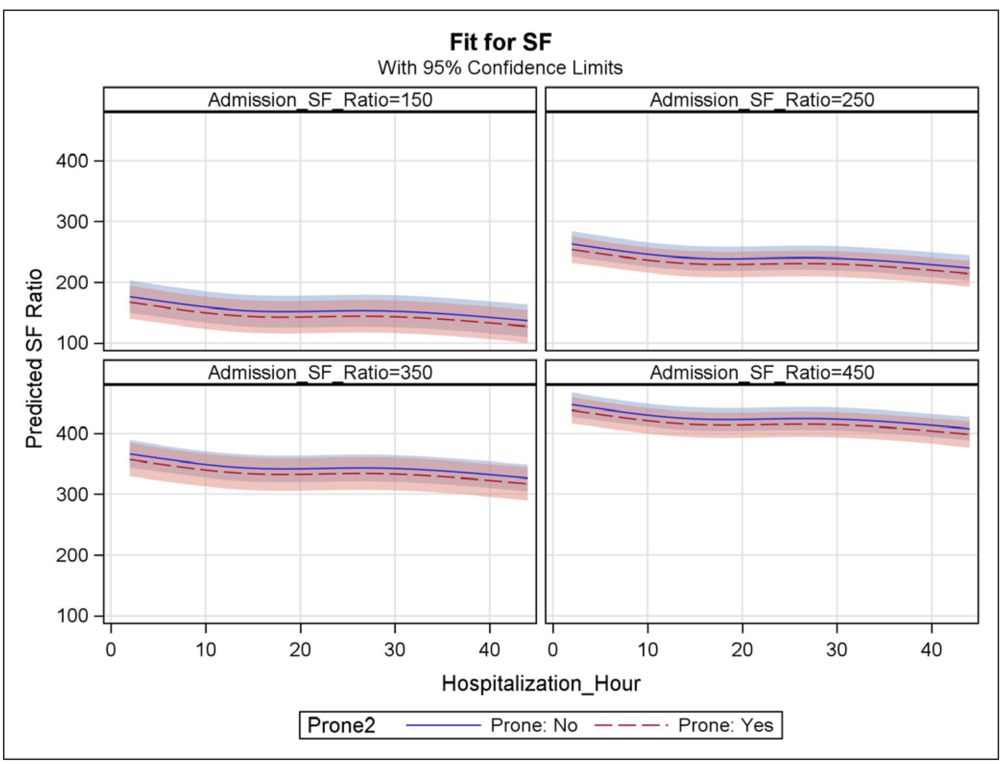

Figure 3. Predicted peripheral capillary oxygen saturation measured by pulse oximetry to the FIO_2 (SF) ratio across hour of hospitalization stratified by prone status and SF ratio at admission. *Shaded areas* represent 95% CIs.

find improved S/F ratios during the first 48 hours of hospitalization in our cohort (27). However, the collection of S/F ratios relative to position was not protocolized, and it is unknown whether each measurement was made prone versus supine. Although it is generally accepted that improved oxygen saturations are sustained when a proned ARDS patient is returned to the supine position, it is possible that the benefits of proning are less durable in COVID-19. If that phenomenon were true, any improvements in S/F ratio with proning would only be evident during proning—and would likely be impossible to discern using retrospective data. Furthermore, the duration of proning was entirely at the patient's discretion, and our dataset renders it impossible for us to compare S/F measurements with adjustment for the length of time a patient had been in a given position when each measurement was recorded.

In addition to these limitations imposed by our retrospective design, it should be reiterated that the practice of self-proning—necessitated by staffing shortages—was not closely monitored by physicians, nurses, respiratory therapists, or using electronic/digital means. This allowed for potential variability in positioning and some "proned" patients may have assumed a more lateral decubitus position as opposed to true prone positioning. Similarly, the extent of movement during proning was not quantified: once proned, some patients were relatively comfortable and stayed still while others were constantly moving to find a more accommodating position. Furthermore, our inclusion criteria for duration of proning required only a "minimum" amount of time—meaning patients lumped together in the "prone" group could have profoundly different lengths of time for positional changes to result in physiologic benefits.

We would argue that, collectively, these study limitations likely result in a conservative estimate of the potential benefits of awake self-proning in COVID-19. The data analyzed represent real-world practice during a pandemic wherein ill patients assumed ownership of this aspect of their care as the overwhelmed healthcare system was simply unable to execute and monitor proning as is the routine with conventional ARDS patients. Further investigation in this realm is needed to confirm our findings prospectively, to assess collateral benefits (reduced use of mechanical ventilation likely reduces the severity of medication shortages), to identify potential drawbacks (impact on staffing needs, adverse effects for patients), and to better quantify the optimal duration of proning.

CONCLUSIONS

In this single-center, retrospective study conducted in a rural hospital with limited resources, awake self-proning was associated with a lower the rate of intubation and lower mortality. Awake proning appears to be a safe, inexpensive, and effective way to improve outcomes and spare limited resources during the COVID-19 pandemic. Further efforts are needed to assess the effect of awake proning on oxygenation and to improve patients' ability to tolerate this intervention.

All authors had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. All authors contributed substantially to the study design, data analysis and interpretation, and the writing of the article.

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