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A Case-Control Study of Prone Positioning in Awake and Nonintubated Hospitalized Coronavirus Disease 2019 Patients

Peter C. Nauka, MD[1]
Sweta Chekuri, MD[2]
Michael Aboodi, MD, MS[3]
Aluko A. Hope, MD, MS[3]
Michelle N. Gong, MD, MS[3]
Jen-Ting Chen, MD, MS[3]

OBJECTIVES: To determine the association between prone positioning in nonintubated patients with coronavirus disease 2019 and frequency of invasive mechanical ventilation or inhospital mortality.

DESIGN: A nested case-matched control analysis.

SETTING: Three hospital sites in Bronx, NY.

PATIENTS: Adult coronavirus disease 2019 patients admitted between March 1, 2020, and April 1, 2020. We excluded patients with do-not-intubate orders. Cases were defined by invasive mechanical ventilation or inhospital mortality. Each case was matched with two controls based on age, gender, admission date, and hospital length of stay greater than index time of matched case via risk-set sampling. The presence of nonintubated proning was identified from provider documentation.

INTERVENTION: Nonintubated proning documented prior to invasive mechanical ventilation or inhospital mortality for cases or prior to corresponding index time for matched controls.

MEASUREMENTS AND MAIN RESULTS: We included 600 patients, 41 (6.8%) underwent nonintubated proning. Cases had lower Spo_2/Fio_2 ratios prior to invasive mechanical ventilation or inhospital mortality compared with controls (case median, 97 [interquartile range, 90–290] vs control median, 404 [interquartile range, 296–452]). Although most providers (58.5%) documented immediate improvement in oxygenation status after initiating nonintubated proning, there was no difference in worst Spo_2/Fio_2 ratios before and after nonintubated proning in both case and control (case median Spo_2/Fio_2 ratio difference, 3 [interquartile range, −3 to 8] vs control median Spo_2/Fio_2 ratio difference, 0 [interquartile range, −3 to 50]). In the univariate analysis, patients who underwent nonintubated proning were 2.57 times more likely to require invasive mechanical ventilation or experience inhospital mortality (hazard ratio, 2.57; 95% CI, 1.17–5.64; $p = 0.02$). Following adjustment for patient level differences, we found no association between nonintubated proning and invasive mechanical ventilation or inhospital mortality (adjusted hazard ratio, 0.92; 95% CI, 0.34–2.45; $p = 0.86$).

CONCLUSIONS: There was no significant association with reduced risk of invasive mechanical ventilation or inhospital mortality after adjusting for baseline severity of illness and oxygenation status.

KEY WORDS: coronavirus infection; hypoxia; inhospital mortality; mechanical ventilation; prone position; respiratory failure

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Prone positioning is a well-established recruitment maneuver that can improve oxygenation and decrease mortality in patients with severe acute respiratory distress syndrome (ARDS) (1–3). Patients with novel coronavirus disease 2019 (COVID-19) frequently present with profound hypoxemia (4–11).

There is evolving literature in utilizing proning in nonintubated COVID-19 patients; however, none of these studies have demonstrated sustained improvement in patient-centered outcomes such as decreased risk of invasive mechanical ventilation (IMV) or improved survival (12–17). Some studies have shown an improvement in oxygenation, but these studies are limited by small study populations and selection bias of healthier patients, and demonstrate nonclinically significant end points such as temporary improvement of oxygenation.

We conducted a large retrospective nested case-matched control study to characterize the oxygenation response in a cohort of COVID-19 patients undergoing nonintubated proning to determine the association of nonintubated proning with patients who develop the composite outcome of IMV or inhospital mortality. We hypothesized that nonintubated proning would not alter the need for IMV and inhospital mortality.

MATERIALS AND METHODS

Study Setting and Population

This study was approved by the Institutional Review Board (IRB) at Albert Einstein College of Medicine (IRB 2020-11278). We performed a retrospective, nested case-control study in a cohort of consecutive adult (≥ 18 years old) patients admitted to three hospitals in the Montefiore Healthcare System between March 1, 2020, and April 1, 2020, with laboratory-confirmed COVID-19 via real-time reverse polymerase chain reaction (RT-PCR) from nasopharyngeal swabs (Cepheid, Sunnyvale, CA; Viracor Eurofins severe acute respiratory syndrome coronavirus 2 RT-PCR, Lees Summit, MO; Quest Diagnostics, Seacaucus, NJ). Patients were excluded if they had a do-not-intubate (DNI) order during the admission, as IMV was an outcome of interest, or if they were admitted to an affiliated hospital and did not have medical records available to the study team.

Matching Case and Control

We defined cases as COVID-19 patients from the above cohort who met the end point of IMV or inhospital mortality during their hospital admission. Index time was defined as the time after hospital admission when the case was intubated or died, whichever came first. Controls were patients who were alive and not on IMV between the hospital admission date and index time of the corresponding case for risk set sampling. From our cohort of COVID-19 positive patients, we matched a case with two available controls by exact age, gender, admission date within 2 weeks of case, and hospital length of stay greater than the duration of time from hospital admission to the index day of the case (18). Matching was performed with replacement; thus, controls could serve as cases for other controls if they were intubated or died. We included all cases that had available controls from the overall COVID-19 cohort.

Exposure: Nonintubated Proning

We manually reviewed the medical chart to extract timing of initiation and cessation of prone positioning from clinician or nursing documentation. Based on risk set sampling, only nonintubated proning documented prior to IMV or inhospital mortality for cases, or prior to corresponding index time for matched controls was included in our statistical analysis.

Data Collection

Patients were identified through electronic health record data abstraction from EPIC (Verona, WI) using Clinical Looking Glass (Clinical Analytics, New York, NY). Baseline demographic and clinical characteristics including age, gender, race, ethnicity, Charlson comorbidity index, body mass index (BMI), and Sequential Organ Failure Assessment (SOFA) score at 24 hours were extracted. We imputed the cohort median BMI for two cases and four controls who had missing data. For SOFA score calculation, the neurology component uses the Glasgow Coma Score, which was not reliably recorded in the electronic medical record; therefore, we assumed zero for normal value for every patient. We calculated Pao_2/Fio_2 ratio for the respiratory SOFA component from Spo_2/Fio_2 (S/F) ratio when arterial blood gas value was not available (19). We also

recorded whether each patient required ICU admission, hospital and ICU lengths of stay, need for IMV, and inhospital mortality.

To obtain a measure of each patient's oxygenation status, we manually extracted the worst S/F ratio prior to IMV or inhospital death for cases, or prior to corresponding index time for matched controls. Nursing staff routinely documents peripheral saturation and corresponding oxygen support. We recorded the lowest S/F ratio available. We used S/F ratio, because arterial blood gas data were not available for all patients (19–22). To determine whether nonintubated proning improved overall oxygenation status, we separately recorded the worst S/F ratio pre- and postinitiation of nonintubated proning on the same calendar day of proning initiation. We recorded whether providers documented an immediate subjective or objective perception of oxygenation improvement (regardless of future outcome) during initiation of nonintubated proning.

Statistical Analysis

Continuous variables were summarized with mean and SD if normally distributed, using median and interquartile range (IQR) for nonparametric distributions.

We performed conditional logistic regression to determine the association of nonintubated proning as the exposure variable on the composite-dependent outcome of IMV or inhospital mortality. We determined a priori to adjust for potential confounders including Charlson comorbidity index, SOFA score, BMI, and worst S/F ratio prior to index time. BMI was also identified given practical challenges of prone positioning morbidly obese patients and prior reported association between obesity and mortality in COVID-19 patients (23–27). We theorized that the worst S/F ratio represented the oxygenation status that would likely directly influence providers' decisions about prone positioning. Hazard ratio (HR) and adjusted HR with 95% CIs were used to summarize association of nonintubated proning with the outcome of interest. We performed a sensitivity analysis using inverse-probability-weighted treatment effect estimators. Statistical analysis was performed using Stata Version 16.1 (StataCorp LLC, College Station, TX). All $p < 0.05$ in a two-tailed test were considered to be statistically significant.

RESULTS

A total of 1,566 eligible patients with COVID-19 admitted between March 1, 2020, and April 1, 2020, were identified (**Fig. 1**). Of those, 348 patients met exclusion criteria, including 274 who had DNI status during admission and 74 who were admitted to an affiliate site and records were not available. Of the eligible 1,218 hospitalized COVID-19 patients, we identified 200 cases with 400 available 1:2 matched controls by age, gender, time of hospital admission, and hospital length of stay greater than the duration of time from hospital admission to the index day of the case. A total of 36 cases also served as matching control for a different pair.

Cohort Characteristics

Cases had a similar proportion of male gender and age compared to the control group (**Table 1**). There were no significant differences in race, ethnicity, or site between the two groups. Cases had a higher median BMI than controls (case median, 29.9 [IQR, 26.5–33.2] vs control median, 29.0 [IQR, 25.6–33.2]). Overall, the cases were sicker than the controls including: higher Charlson comorbidity index (case median, 2 [IQR, 0–5] vs control median, 1 [IQR, 0–4]), worse SOFA score at 24 hours from admission (case median, 4 [IQR, 1.5–7] vs control median, 1 [IQR, 0–2]), and lower S/F ratio prior to index time (case median, 97 [IQR, 90–290] vs control median, 404 [IQR, 296–452]).

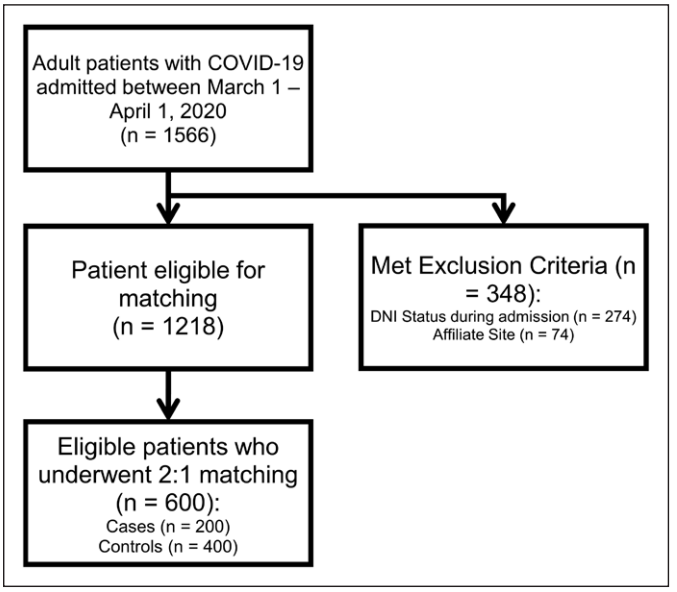

Figure 1. Flowsheet of eligible patients who underwent matching. COVID-19 = coronavirus disease 2019, DNI = do-not-intubate.

TABLE 1.
Baseline and Demographic Characteristics of Cohort

Variable	Total Cohort	Case ($n = 200$)	Control ($n = 400$)
Age (yr), mean (SD)	61.2 (13.1)	61.6 (13.0)	60.9 (13.1)
Body mass index (kg/m^2), median (IQR)[a]	29.3 (25.8–33.9)	29.9 (26.5–35.6)	29.0 (25.6–33.2)
Male sex, *n* (%)	372 (62)	123 (61.5)	249 (62.3)
Ethnicity, *n* (%)			
Spanish/Hispanic/Latino	199 (33.2)	66 (33.2)	133 (33.3)
Not Spanish/Hispanic/Latino	329 (54.8)	111 (55.5)	218 (54.5)
Other/not specified	72 (12.0)	23 (11.6)	49 (12.3)
Race, *n* (%)			
Black/African-American	247 (41.2)	76 (38.0)	171 (42.8)
Asian	20 (3.3)	10 (5.0)	10 (2.5)
White	54 (9.0)	12 (6.0)	42 (10.5)
Other/not specified	279 (46.5)	102 (51.0)	177 (44.2)
Hospital campus, *n* (%)			
Moses	309 (51.5)	98 (49.0)	211 (52.8)
Wakefield	130 (21.7)	41 (20.5)	89 (22.3)
Weiler	161 (26.8)	61 (30.5)	100 (25.0)
Charlson comorbidity index, median (IQR)	2 (0–4)	2 (0–5)	1 (0–4)
Sequential Organ Failure Assessment score in 24 hr prior to index time, median (IQR)	1 (0–4)	4 (1.5–7)	1 (0–2)
Worst Spo_2/Fio_2 ratio prior to index time, median (IQR)[b]	346 (99–443)	97 (90–290)	404 (296–452)
Highest level of respiratory support prior to index time, *n* (%)[c]			
HiFlow	56 (9.4)	40 (20.5)	16 (4.0)
NRB	139 (23.4)	90 (46.2)	49 (12.2)
NC	183 (30.8)	27 (13.9)	156 (39.0)
RA	217 (36.4)	38 (19.4)	179 (44.8)
Admission C-reactive protein (< 0.8 mg/dL), median (IQR)[d]	13.1 (5.7–21.2)	17.6 (8.2–29.6)	11.3 (4.7–16.8)
Admission D-dimer (0.0–0.5 ug/mL), median (IQR)[e]	1.49 (0.72–3.11)	2.63 (1.36–7.76)	1.03 (0.67–2.3)

(*Continued*)

TABLE 1. (*Continued*).
Baseline and Demographic Characteristics of Cohort

Variable	Total Cohort	Case (*n* = 200)	Control (*n* = 400)
Underwent prone positioning at any point during admission, *n* (%)[f]	164 (27.3)	84 (42.0)	80 (20.0)
Prone positioning on RA	4 (0.7)	0 (0)	4 (1.0)
Prone positioning on NC	36 (6.0)	3 (1.5)	33 (8.3)
Prone positioning on NRB	55 (9.2)	19 (9.5)	36 (9.0)
Prone positioning on HiFlow	24 (4.0)	10 (5.0)	14 (3.5)
Prone positioning on MV	86 (14.3)	61 (30.5)	25 (6.3)
Length of prone positioning, d (IQR)	2 (1–6)	2 (1–6)	3 (1–6.5)
Time from admission to prone positioning, hr (IQR)	79.9 (34.7–126.2)	68.8 (21.6–111.8)	88.7 (53.7–137.8)
Required ICU admission, *n* (%)	174 (29.0)	117 (58.5)	57 (14.3)
Hospital LOS (d), median (IQR)	7.0 (4.2–12.1)	6.7 (3.8–16.2)	7.0 (4.3–11.6)
ICU LOS (d), median (IQR)	6.4 (3.7–13.0)	6.9 (3.9–13.8)	5.8 (3.3–12.8)
Composite event (MV or mortality), *n* (%)	290 (48.3)	200 (100)	90 (22.5)
MV	247 (41.2)	175 (88.4)	72 (18.1)
Mortality	209 (34.8)	147 (73.5)	62 (15.5)

HiFlow = high-flow nasal cannula, IQR = interquartile range, LOS = length of stay, MV = mechanical ventilation, NC = nasal cannula, NRB = nonrebreather mask, RA = room air.

[a]Body mass index data were missing for six patients.

[b]Worst Spo_2/Fio_2 (S/F) ratio on highest oxygen device prior to time to invasive mechanical ventilation or death for cases or index time for matched controls. In five cases, patient was intubated shortly after arrival and preintubation S/F ratio was not available. For those instances, first available S/F ratio was used.

[c]There were five case patients who were intubated shortly after arrival and the first available S/F ratio on ventilator was used. These patients are not reflected in percentages.

[d]Admission C-reactive protein (CRP) was defined as the first available value within 48 hr of admission. There were 207 patients with available admission CRP.

[e]Admission D-dimer was defined as the first available value within 48 hr of admission. There were 206 patients with available admission D-dimer.

[f]Prone positioning could occur at any point during admission, including after mechanical ventilation initiation. Patients could undergo prone positioning on multiple types of oxygen support.

A total of 42.0% of cases underwent prone positioning at any time, regardless of respiratory support device types during their admission, as compared with only 20.0% of control group patients. Prone positioning after intubation was implemented on 86 subjects (14.3%). More cases required ICU admission than the control group (Table 1).

A total of 90 controls (22.5%) met the composite outcome of IMV or inhospital mortality at some point during admission after their case-matched index time (Table 1). A total of 247 patients (41%) were mechanically ventilated, including 175 cases (88%) and 72 controls (18%). A total of 38 cases (19.4%) were intubated urgently shortly after initial presentation; therefore, their highest level of oxygen support prior to intubation was room air. Median length of stay was similar between the two groups (Table 1).

Nonintubated Proning in the Cases and Controls

There were 41 patients who underwent nonintubated proning prior to index time (**Table 2**). A higher proportion of cases underwent nonintubated proning (case: 20 [10.0%] vs control: 21 [5.3%]). Cases underwent nonintubated proning substantially later than controls during admission (time difference, 11.6 hr [IQR, 12.6–40.5 hr]) (Table 2). Cases were maintained on nonintubated proning for less time compared with controls (time difference, 39.2 hr [IQR, 0–88.9 hr]) (Table 2). A majority of both case and control patients required a nonrebreather mask for oxygen support during nonintubated proning (cases: 12 [60.0%] vs control: 14 [66.7%]) (Table 2). Prior to initiation of nonintubated proning, S/F ratios were lower for cases than controls (Table 2). The worst S/F ratio after nonintubated proning was similar to the ratio prior to nonintubated proning on the same calendar day in both cases and controls (case: S/F ratio difference 3 [IQR, –3 to 8] and control: S/F ratio difference, 0 [IQR, –3 to 50]) (Table 2). Furthermore, the difference in S/F ratios before and after nonintubated proning was similar between the cases and controls (Table 2). In both case (60.0%) and control (57.1%) groups, a majority of providers documented perceived improvement in patient oxygenation status after nonintubated proning.

Association Between Nonintubated Proning and IMV or Inhospital Mortality

In our univariate analysis, patients who underwent nonintubated proning were 2.57 times more likely to require IMV or expire during hospitalization (HR, 2.57; 95% CI, 1.17–5.64; p = 0.02) (**Table 3**, and

TABLE 2.
Oxygenation Characteristics of Patients Undergoing Nonintubated Proning

Variable	Total Cohort	Case (n = 200)	Control (n = 400)
Nonintubated proning	41 (6.8%)	20 (10.0%)	21 (5.3%)
Time from admission to nonintubated proning, hr (IQR)	51.1 (23.5–79.3)	61.2 (25.9–87.3)	41.9 (18.1–74.3)
Time on nonintubated proning, hr (IQR)	33.8 (5.1–96.9)	19.2 (4.8–40.3)	72.2 (20.1–124.4)
Oxygen requirement on nonintubated proning, *n* (%)			
High-flow nasal cannula	12 (29.3)	8 (40.0)	4 (19.0)
Nonrebreather mask	26 (63.4)	12 (60.0)	14 (66.7)
Nasal cannula	3 (7.3)	0 (0)	3 (14.3)
Worst S/F ratio prior to nonintubated proning[a] (IQR)	95 (93–133)	93 (91–97)	98 (95–294)
Worst S/F ratio after nonintubated proning initiation (IQR)[b]	95 (92–100)	93 (89–96)	97 (95–104)
S/F ratio difference between pre- and post-nonintubated pronings[c] (IQR)	2 (–3 to 9)	3 (–3 to 8)	0 (–3 to 50)
Perception of improvement[d]	24 (58.5)	12 (60.0)	12 (57.1)

IQR = interquartile range, S/F = Spo_2/Fio_2 ratio.

[a]Worst S/F ratio on the same calendar day but prior to initiation of prone positioning. Worst S/F ratio on the highest level of oxygen support was used.

[b]Worst S/F ratio on the same calendar day but after initiation of prone positioning. Worst S/F ratio on the highest level of oxygen support was used.

[c]*p* value represents change pre- and postinitiation of nonintubated proning for cases and controls individually. A positive S/F ratio indicates improvement in oxygenation.

[d]Includes any objective or subjective provider documentation of improvement in patient's oxygenation status as a direct result of prone positioning.

TABLE 3.
Unadjusted and Adjusted Hazard Ratios on Composite Outcome of Mechanical Ventilation or Mortality

Association With Invasive Mechanical Ventilation/Inhospital Mortality	Unadjusted HR	*p*	Adjusted HR[a]	*p*
Nonintubated proning	2.57 (1.17–5.64)	0.02	0.92 (0.34–2.45)	0.86
Body mass index[b]	1.03 (1.00–1.05)	0.02	1.03 (0.99–1.07)	0.10
Charlson comorbidity index	1.14 (1.07–1.23)	< 0.001	1.06 (0.95–1.19)	0.26
Worst Spo_2/Fio_2 ratio[c]	0.92 (0.91–0.94)	< 0.001	0.92 (0.90–0.94)	< 0.001
Sequential Organ Failure Assessment score at 24 hr	1.52 (1.40–1.66)	< 0.001	1.45 (1.28–1.65)	< 0.001

HR = hazard ratio.

[a]Adjusted for body mass index, baseline Charlson comorbidity index, worst Spo_2/Fio_2 (S/F) ratio, and 24-hr Sequential Organ Failure Assessment score. Individual odds ratios for each contributing to adjustment are presented below. Final model contained 572 observations. A total of 22 observations were removed due to negligible contribution to model and six observations were not included due to missing body mass index (BMI) information.

[b]BMI data were missing from six patients.

[c]Odds ratio corresponds to an increase in Spo_2/Fio_2 ratio by 10.

Supplementary Fig. 1, http://links.lww.com/CCX/A499). After adjustment with Charlson comorbidity index, BMI, worst S/F ratio, and SOFA score, we found no association between nonintubated proning and IMV or inhospital mortality (adjusted HR, 0.92; 95% CI, 0.34–2.45; $p = 0.86$). We saw that for every increase by 10 in worst S/F ratio prior to index time, the odds of IMV or inhospital mortality decreased by 8% (adjusted HR, 0.92; 95% CI, 0.90–0.94; $p < 0.001$). Inversely, with every 1-point increase in SOFA score, the odds of IMV or inhospital mortality increased by 45% (adjusted HR, 1.45; 95% CI, 1.28–1.65; $p < 0.001$) (Table 3).

In our sensitivity analysis, nonintubated proning average treatment effect was –0.03 (–0.20, 0.14) and average treatment effect on the treated was –0.9 (–0.22, 0.03). Nonintubated proning did not affect the probability of IMV or inhospital mortality.

DISCUSSION

In this large case-matched control study of COVID-19 patients, nonintubated proning was not associated with a decrease in IMV or inhospital mortality. Prone positioning was used more frequently in COVID-19 patients with acute hypoxemic respiratory failure than previously reported in ARDS literature (Lung Safe and Severe ARDS: Generating Evidence trials) and was employed on a wide range of respiratory support devices not limited to IMV (28–30). Although the cases were more likely to undergo nonintubated proning, they were significantly more hypoxemic and at higher risk for clinical deterioration compared with the controls. After adjusting for patient-level difference, nonintubated proning was not associated with IMV or inhospital mortality.

We saw an increase in the utilization of prone positioning in patients with acute hypoxemic respiratory failure on IMV in this cohort. The patients who underwent prone positioning while on IMV were likely in moderate-to-severe ARDS, supported by their median worst S/F ratio. The use of prone positioning as an adjunctive therapy is more prominent than previous large epidemiologic reports of moderate-to-severe ARDS patients, where the use of prone positioning ranged from 7.0% to 11.6% with higher utilization in more hypoxic patients (16.3% in the severe ARDS population from the Lung Safe Study) (28–30). Historically, prone positioning was rarely used at our institution. The COVID-19 pandemic has accelerated our adoption of this evidence-based therapy.

Prior reports on nonintubated proning have demonstrated an immediate physiologic benefit, including improvement in oxygen saturation, alleviation of dyspnea, and decreasing respiratory rate, but

it remains unclear if this translates to improved clinical outcomes. Oxygen benefit does not appear to be universal for all COVID-19 patients, and up to half may desaturate after resupination (14, 16). A recent prospective cohort study noted that addition of nonintubated proning to high-flow nasal cannula therapy did not prevent IMV or mortality (31). Many awake patients do not tolerate extended nonintubated proning. Nonintubated proning of 16 hours or greater has been examined but may not be practicable with most patients (31). About 58.5% of providers documented immediate improvement in oxygenation, but we noted no sustained improvement in S/F ratios following nonintubated proning. Our finding supports the notion that transient improvement in oxygenation may not be associated with overall improvement in patients with acute respiratory failure at risk for IMV and inhospital mortality.

Concerningly, the strong relationship between worst S/F ratios, SOFA scores, and nonintubated proning suggests that providers are most likely to prone patients at risk of clinical deterioration. This could potentially lead to delaying the initiation of IMV in patient at highest risk. Patients undergoing nonintubated proning have been identified to undergo a delay to intubation (31). Numerous reports have suggested that delaying intubation for patients with hypoxemic respiratory failure may increase morbidity and mortality (32–35). Spontaneously breathing patients with ARDS have a high work of breathing with significant tidal volume, which may induce spontaneous lung injury (36, 37). Delaying intubation in patients with respiratory failure may result in worsening and persistent hypoxemia, which is linked to increased mortality (38–40). In contrast, several recent reports have indicated that both hypoxic COVID-19 and nonCOVID-19 patients on high-flow nasal cannula may derive benefit or at least have no harm from delayed intubation (41, 42). It remains unclear if delaying intubation with nonintubated proning will improve or worsen survival in COVID-19 ARDS.

Intubated patients with mild-to-moderate ARDS are unlikely to benefit from prone positioning. Many studies that included mechanically ventilated patients with mild or moderate levels of ARDS failed to demonstrate any benefit to prone positioning (3, 43–46). The Proning Severe ARDS Patients trial only conclusively demonstrated a mortality benefit in severe ARDS (3). An outcome benefit has never been proven in patients with mild ARDS. We found that proning of nonintubated patients was not beneficial, likely due to a milder degree of hypoxemic respiratory failure at the time of nonintubated proning. We also noted that patients in the case group underwent nonintubated proning approximately 20 hours later than controls and remained on nonintubated proning for a shorter duration. It is possible that earlier initiation may have resulted in clinical benefit.

The diverse oxygen support modes used during nonintubated proning reflect a lack of consensus to attempt such procedures and indicate an urgent need for robust, randomized trials to further elucidate appropriate indications for nonintubated proning. Nonintubated proning may also limit mobility in this subgroup of patients, which may lead to heightened venous thromboembolism risk given reports of increased venous thromboembolism in COVID-19 (47, 48).

This case-matched control analysis had some limitations. We included a heterogeneous population with various oxygenation requirements across various support devices, which may have limited our ability to detect clinical improvements. We used S/F ratio to represent the severity of hypoxemia instead of the traditional Pao_2-to-Fio_2 ratio, as most patients did not have arterial blood gas values. Although many patients underwent prone positioning at some point during their admission, only a minority qualified as nonintubated proning. The frequency of nonintubated proning was lower than expected, which may have limited our power in detecting an effect of the treatment. However, in our sensitivity analysis, we did not observe a treatment effect. As prone positioning was identified based on subjective documentation, we could not verify patient adherence to nonintubated proning or obtain the number of hours per day that nonintubated proning was maintained. However, our approach likely represents an accurate real-world clinical application of nonintubated proning as strict patient adherence to 16 hours of awake proning may not be possible. As with all retrospective analyses, we cannot exclude the possibility of unmeasured confounders. Using incident density sampling, a case could serve as a control for another matched pair; thus, the controls may not be completely generalizable to the whole cohort. We accounted for the between group correlation by conditional logistic

regression. Adjusting for forward clinical trajectory of patients is difficult, and we did not adjust for inflammatory laboratory markers that are known to predict mortality in COVID-19 patients. Based on our clinical experiences, physicians are more likely to prone position patients based on oxygenation status rather than inflammatory markers. Institutional guidelines suggested using nonintubated proning for COVID-19 patients with hypoxemic respiratory failure, but this was not mandatory. The application of this maneuver likely differed by physician preference. Strengths of our analysis include a large sample size, robust statistical design, and controlling for many likely confounders. A nested case-control design was used to reduce confounding via matching and decrease influence of immortal time bias. We studied a clinically relevant end point that improves the generalizability of our finding.

CONCLUSIONS

Prone positioning among nonintubated spontaneously breathing COVID-19 patients was not associated with the need for IMV or inhospital mortality in our large, nested case-control cohort. Although nonintubated proning may temporarily improve hypoxemia, physicians should not expect this maneuver to change the course of the disease. Nonintubated proning may be appropriate in select populations, especially during pandemic conditions with limited resources, but physicians should rigorously monitor respiratory parameters since prolonged and unrecognized hypoxemia could lead to more complicated intubations and worse outcomes in patients with respiratory failure. Indeed, we saw that intubation rates did not appear to be altered with nonintubated proning. Further large-scale prospective trials are urgently needed to further elucidate whether nonintubated proning can ameliorate mortality and IMV in COVID-19 patients.

1 *Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Internal Medicine Residency Program, Bronx, NY.*

2 *Department of Medicine, Division of Hospital Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY.*

3 *Department of Medicine, Division of Critical Care, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.*

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All authors contributed to study conception, design, data acquisition, and analysis preparation of this article.

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For information regarding this article, E-mail: jeche@montefiore.org

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