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Original Article

# Use of the Prone Position in Critically Ill COVID-19 Patients: Can the Response Be Predicted?

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SUMMARY

*Background:* Coronavirus disease 2019 (COVID-19) can cause acute respiratory failure and acute respiratory distress syndrome (ARDS). The prone position (PP) is widely used in patients with severe hypoxemia due to ARDS as it improves oxygenation. The aim of this study was to investigate whether improvements in gas exchange and lung mechanics with the PP were associated with survival in ventilated COVID-19 patients.

*Methods:* Fourteen ventilated patients who were placed in the PP were included from May to June 2021. Clinical manifestations and lung mechanics parameters were collected.

*Results:* The overall intensive care unit (ICU) mortality rate was 42.9%. Nonsurvivors were older ($p$ = 0.014) and had higher Charlson comorbidity index (2.1 ± 1.5 vs. 4.8 ± 2.4, $p$ = 0.035) and Sepsis-related Organ Failure Assessment (SOFA) (3.3 ± 1.0 vs. 7.3 ± 3.5, $p$ = 0.019) scores compared to survivors. There was no difference in $PaO_2/FiO_2$ (P/F ratio) at baseline between the survivors and nonsurvivors. The improvement in P/F ratio ($p$ = 0.0037) and reduction in driving pressure (Pdrive) ($p$ = 0.046) on the second day after first PP were correlated with lower mortality. Significant predictors of successfully stopping prone treatment included a reduction in Pdrive at the first hour, lower tidal volume (Vt) at the fourth hour, and P/F ratio improvement on the second day after PP.

*Conclusion:* Improvement in P/F ratio and reduction in driving pressure on the second day after PP were correlated with reduced mortality. Three parameters could predict successful resumption of the supine position.



## 1. Introduction

The novel beta-coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-COV-2)[1] causes coronavirus disease 2019 (COVID-19) which has been a global pandemic since 2019. COVID-19 has been reported to cause acute respiratory failure in a significant portion of patients, some of whom subsequently develop acute respiratory distress syndrome (ARDS).[2,3]

ARDS is an acute, diffuse, inflammatory form of lung injury which is associated with high rates of morbidity and mortality.[4,5] Several management strategies are currently used, including lung protective ventilation, neuromuscular blocking agents, steroids[6] and even extracorporeal membrane oxygenation (ECMO). However, the mortality rate of patients with severe ARDS remains around 40%.[5]

The prone position (PP) has been widely used as an alternative approach for patients with severe hypoxic respiratory failure for decades.[7–9] The PP is easily performed after brief training at minimal cost and without the need for special equipment. It has been shown to improve oxygenation,[9,10] respiratory mechanics,[11] homogenize the pleural pressure gradient,[12] increase lung volume over functional residual capacity, and reduce the number of atelectatic regions. It has also been shown to facilitate the drainage of secretions and reduce ventilator-induced lung injury.[13] Guérin et al.[7] reported that use of the PP could significantly reduce 28-day and 90-day mortality of patients with severe ARDS. However, its application in COVID-19-related ARDS remains inconclusive. There are several concerns about its use in COVID-19 patients. First, the PP maneuver completely relies on manpower, and three to four members of staff are usually needed.[7] This number of staff in a small space increases the risk of contamination. Second, the optimal duration of each PP session is unconclusive, although the current consensus is 16–20 hours a day until the patient's condition improves.[14] Frequently turning the patient over may also increase the risk of contamination and increase the use of personal protective equipment.

Despite the many restrictions, pandemics force physicians to use any available options to manage their hypoxic patients.[15] Early application of the PP,[16] prolonged use of the PP[10] and awake PP[17] have been proposed as potential management options for patients with COVID-19-induced ARDS, however the timing and duration of PP remain uncertain. Therefore, the aim of this study was to analyze the correlation between PP efficacy and clinical outcomes in patients

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with COVID-19-induced ARDS during the latest outbreak in Taiwan.

## 2. Patients and methods

This retrospective, single-center cohort study was conducted at a referral center in northwest Taipei with 24-bed negative pressure quarantine intensive care unit (ICU).

From May to June 2021, 39 critically ill COVID-19 patients were admitted to our ICU for acute respiratory failure requiring mechanical ventilation support. All patients were confirmed by a positive reverse-transcriptase-polymerase chain reaction (RT-PCR) assay of a respiratory specimen. Fourteen of them developed severe ARDS, which was defined as $PaO_2/FiO_2$ (P/F ratio) < 150 according to the Berlin definition.[4] All of these patients received PP management during their hospital stay, and baseline demographics, associated comorbidities, laboratory tests, lung mechanics parameters during mechanical ventilation, and clinical outcomes were collected.

The elderly group was defined as patients aged 65 years and older. Obesity was defined as a body mass index (BMI) above 27 $kg/m^2$, according to the Ministry of Health and Welfare of Taiwan. The Charlson comorbidity index (CCI)[18] was used to assess the degree of comorbidity, and the Acute Physiologic and Chronic Health Evaluation II (APACHE II) score was used to evaluate the severity of disease.[19] The Sepsis-related Organ Failure Assessment (SOFA) score was used to evaluate the degree of dysfunction or organ failure caused by infection.[20] Variables including P/F ratio, positive end-expiratory pressure (PEEP) level, tidal volume per predicted body weight (Vt/PBW), static compliance of the respiratory system (Crs), plateau pressure (Pplt), driving pressure (Pdrive) were measured at baseline, at the first hour, fourth hour, first day, second day of the PP, and after resuming the supine position.

### 2.1. Outcome measurements

The primary outcome was ICU mortality, and the secondary outcome was successful termination of PP, which defined as a P/F ratio $\geq$ 150 mmHg with PEEP $\leq$ 10 $cmH_2O$ and $FiO_2 \leq 0.6$ after resuming the supine position for at least 4 hours, as reported in the ProSEVA trial.[7]

### 2.2. Statistical analysis

Continuous variables were presented as mean and standard deviation (SD), and categorical variables were presented as percentage. Comparisons between survivor and nonsurvivor groups were analyzed using the Mann-Whitney test and chi-square test. The P/F ratio was measured before the patients were placed in the PP, at the first hour, fourth hour, first day and second day during PP, and after resuming the supine position. Correlations between the P/F ratio and variables were analyzed using Pearson's correlation coefficients and bivariate logistic analysis. Correlations between P/F ratio measurements at each time point of prone treatment with time, demographics, clinical parameters, and the error of repeated measurement estimated parameters were analyzed using generalized estimating equations. All statistical analyses were performed using SPSS software, version 25.0 (SPSS Inc. Chicago, IL, USA).

### 2.3. Ethical approval and informed consent

The Ethics Committee of the Mackay Memorial Hospital Institutional Review Board approved this study with approval number of 21MMHIS330e.

## 3. Results

During the study period, 14 ventilated COVID-19 patients who received PP management for severe ARDS were included (mean age 64.5 years; 10 males). Eight of them received only one session of PP, while the others received two sessions of PP. Three patients who received one session of PP died, while three patients who received two sessions of PP died (Figure 1). The overall ICU mortality rate was 42.9%. The patients had an mean BMI of 29.0 ($kg/m^2$), CCI of 3.2, APACHE II score of 22.0, and SOFA score of 5.0, which reflected the severity of disease (Table 1). There were eight patients in the survivor group and six patients in the nonsurvivor group. The nonsurvivors were significant older (57.6 $\pm$ 12.6 vs. 73.6 $\pm$ 5.8 years, $p$ = 0.035) and had higher CCI (2.1 $\pm$ 1.5 vs. 4.8 $\pm$ 2.4, $p$ = 0.035) and SOFA (3.3 $\pm$ 1.0 vs. 7.3 $\pm$ 3.5, $p$ = 0.019) scores compared to the survivors. The nonsurvivors also had a significantly higher level of ferritin (253 $\pm$ 240 vs. 1153 $\pm$ 261 ng/mL, $p$ = 0.050), indicating higher inflammatory status. The other inflammatory biomarkers were similar between the survivors and nonsurvivors, including lactic dehydrogenase and C-reactive protein.

The interval between disease onset to severe ARDS was 7.71 $\pm$ 3.4 days in the whole cohort. The mean time delay from the diagnosis of severe ARDS to use of the PP was 2.8 days. Oxygenation improved in both the survivors and nonsurvivors after PP, however the survivors had a greater improvement. The P/F ratio remained above 150 in the survivor group, whereas it fell to below 150 in the nonsurvivor group (Figure 2). There was a trend of improved oxygenation after PP, and it was correlated with a reduction in mortality ($p$ = 0.06), however it did not reach statistical significance.

The mean duration of the first session of PP was significantly longer in the nonsurvivors than in the survivors (114.33 $\pm$ 46.98 vs. 54.75 $\pm$ 28.07 hours, $p$ = 0.020). The improvement in P/F ratio ($p$ = 0.0037) and reduction in Pdrive ($p$ = 0.046) on the second day after first PP were correlated with ICU mortality. Pdrive persistently decreased in the survivors and gradually increased in the nonsurvivors, however the results did not reach statistical significance (Figure 3).

We then analyzed the baseline respiratory mechanics and ventilator-derived parameters, which showed (mean values): P/F ratio 90.9, Vt 8.2 ml of PBW, PEEP level 8.8 $cmH_2O$, Crs 37.7 $ml/cmH_2O$, Pplt 23.8 $cmH_2O$, and Pdrive 13.8 $cmH_2O$. These variables dynamically changed after PP, including down-titration of $FiO_2$ and PEEP level, with a decline in Vt/PBW from 8.24 to 7.38 mL/kg. This represented low tidal volume ventilation in ARDS, which is defined as a maximal tidal volume of 6–8 ml/kg.[21] Pplt and Pdrive remained under 30[22] and 15[23] $cmH_2O$, respectively, which met the criteria of a protective lung strategy (Table 2).

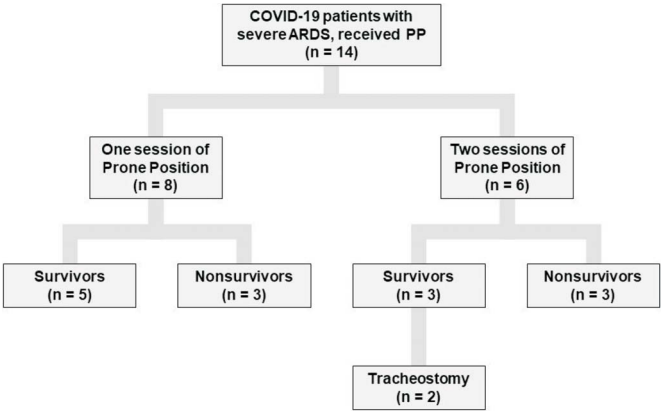


**Figure 1.** Flowchart of the included patients. ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; PP: prone position.

**Table 1**
Patient demographics.

| | All (n = 14) | Survivors (n = 8) | Nonsurvivors (n = 6) | *p* value |
|---|---|---|---|---|
| Age (years) | 64.5 ± 12.9 | 57.6 ± 12.6 | 73.6 ± 5.8 | 0.014 |
| Elderly (≥ 65 years) | 8 (57.1%) | 2 (25.0%) | 6 (100.0%) | 0.007 |
| Gender | | | | |
| Male | 10 (71.4%) | 5 (62.5%) | 5 (83.3%) | 0.548 |
| BMI, kg/m$^2$ | 29.0 ± 9.0 | 30.2 ± 7.0 | 27.3 ± 11.7 | 0.121 |
| Obesity (BMI ≥ 27 kg/m$^2$) | 6 (42.9%) | 4 (50.0%) | 2 (33.3%) | 0.411 |
| Charlson comorbidity index | 3.2 ± 2.3 | 2.1 ± 1.5 | 4.8 ± 2.4 | 0.035 |
| Comorbidity | | | | |
| Chronic lung disease | 2 (14.3%) | 1 (12.5%) | 1 (16.7%) | 0.832 |
| Heart disease | 2 (14.3%) | 0 (0.0%) | 2 (33.3%) | 0.089 |
| Chronic kidney disease | 1 (7.1%) | 0 (0.0%) | 1 (16.7%) | 0.248 |
| Hypertension | 8 (57.1%) | 3 (37.5%) | 5 (83.3%) | 0.098 |
| Diabetes | 5 (35.7%) | 2 (25.0%) | 3 (50.0%) | 0.352 |
| Clinical parameters | | | | |
| APACHE II score | 22.0 ± 9.4 | 20.8 ± 8.5 | 23.6 ± 11.1 | 0.604 |
| SOFA score | 5.0 ± 3.1 | 3.3 ± 1.0 | 7.3 ± 3.5 | 0.019 |
| Laboratory test data | | | | |
| D-dimer, ng/mL | 2490 ± 3072 | 2587 ± 337 | 2247 ± 2532 | 0.699 |
| Ferritin, ng/mL | 703 ± 541 | 253 ± 240 | 1153 ± 261 | 0.050 |
| LDH, U/L | 463 ± 130 (N = 9) | 425 ± 122 | 599 ± 0.0 | 0.142 |
| CRP, mg/dL | 9.6 ± 8.9 (N = 10) | 7.0 ± 5.8 | 15.5 ± 13.5 | 0.425 |
| CT value at diagnosis | 22.0 ± 5.3 (N = 13) | 23.4 ± 6.2 | 19.8 ± 2.8 | 0.187 |
| Time interval | | | | |
| Onset of severe ARDS time, days | 7.71 ± 3.4 | 7.00 ± 2.07 | 8.67 ± 4.59 | 0.234 |
| Severe ARDS to PP time, days | 2.80 ± 3.83 | 1.63 ± 3.42 | 4.38 ± 4.08 | 0.185 |
| PPsession | | | | |
| 1$^{st}$ session duration, hours | 80.29 ± 47.01 | 54.75 ± 28.07 | 114.33 ± 46.98 | 0.020 |
| 2$^{nd}$ session duration, hours | 49.50 ± 20.55 | 58.33 ± 14.74 | 40.67 ± 24.58 | 0.275 |

APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: adult respiratory distress syndrome; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: cycle threshold; LDH: lactic dehydrogenase; PP: prone position; SOFA: Sequential Organ Failure Assessment.

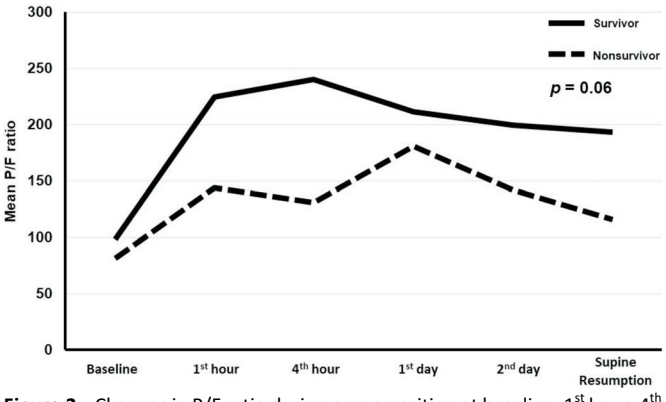


**Figure 2.** Changes in P/F ratio during prone position at baseline, 1$^{st}$ hour, 4$^{th}$ hour, 1$^{st}$ day, 2$^{nd}$ day and resumption of the supine position. There was a trend of improved oxygenation after the prone position which was correlated with a reduction in mortality; however, it did not reach statistical significance. P/F ratio: PaO2/FiO2 ratio.

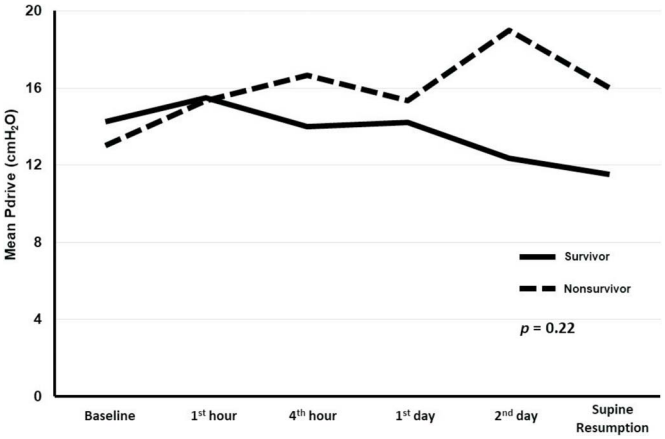


**Figure 3.** Pdrive at baseline, 1$^{st}$ hour, 4$^{th}$ hour, 1$^{st}$ day, 2$^{nd}$ day and resumption of the supine position. Pdrive persistently decreased in the survivors but gradually increased in the nonsurvivors; however, the results did not reach statistical significance. Pdrive: driving pressure.

**Table 2**
Mechanical ventilation and prone position variables at baseline, 1$^{st}$ hour, 4$^{th}$ hour, 1$^{st}$ day, 2$^{nd}$ day and resumption of the supine position.

| | Baseline | 1$^{st}$ hour | 4$^{th}$ hour | 1$^{st}$ day | 2$^{nd}$ day | Supine |
|---|---|---|---|---|---|---|
| $FiO_2$ | 0.83 ± 0.20 | 0.82 ± 0.19 | 0.70 ± 0.22 | 0.60 ± 0.18 | 0.59 ± 0.11 | 0.49 ± 0.10 |
| PEEP, $cmH_2O$ | 9.71 ± 1.54 | 10.00 ± 1.63 | 9.67 ± 1.67 | 10.00 ± 1.48 | 10.00 ± 1.51 | 7.55 ± 2.21 |
| Vt/PBW, mL/kg | 8.24 ± 0.75 | 7.97 ± 0.84 | 7.73 ± 0.80 | 7.65 ± 0.83 | 7.60 ± 0.83 | 7.38 ± 0.61 |
| P/F ratio | 90.29 ± 38.05 | 193.46 ± 110.14 | 181.82 ± 93.90 | 195.92 ± 90.46 | 161.13 ± 59.46 | 187.82 ± 74.90 |
| Crs, mL/$cmH_2O$ | 37.71 ± 19.55 | 42.38 ± 26.22 | 39.64 ± 12.31 | 37.85 ± 14.17 | 34.09 ± 13.44 | 36.70 ± 9.04 |
| Pplt, $cmH_2O$ | 23.83 ± 3.76 | 26.00 ± 2.58 | 24.57 ± 3.87 | 24.13 ± 4.39 | 23.20 ± 4.15 | 20.67 ± 4.16 |
| Pdrive, $cmH_2O$ | 13.83 ± 2.32 | 15.43 ± 3.41 | 15.14 ± 4.45 | 14.63 ± 4.34 | 15.00 ± 4.12 | 13.00 ± 2.65 |

Crs: static compliance of the respiratory system; $FiO_2$: fraction of inspired oxygen; Pdrive: driving pressure; PEEP: positive end-expiratory pressure; P/F ratio: $PaO_2/FiO_2$ ratio; Pplt: plateau pressure; Vt/PBW: tidal volume/predicted body weight.

The predictors of successful termination of PP were: reduction in Pdrive at the first hour (Pearson correlation coefficient = -0.84, $p$ = 0.035), lower Vt at the fourth hour (Pearson correlation coefficient = -0.76, $p$ = 0.017), and improvement in P/F ratio on the second day (Pearson correlation coefficient = 0.71, $p$ = 0.032).

## 4. Discussion

Age is a risk factor for developing life-threatening infections[24] and the development of ARDS.[25] A previous study[26] reported a disproportionately higher rate of COVID-19-related mortality in elderly adults. In addition, another study reported a high mortality rate in ventilated COVID-19 patients, and especially in elderly adults even with intensive care.[27] Several hypotheses[24] have been proposed to explain the severity of COVID-19-induced ARDS in elderly adults, including DNA hypomethylation of regulator T cells, mitochondrial dysfunction and cellular senescence, which cause a cytokine storm and excessive recruitment in the lungs. Taken altogether, similarly to our results, elderly and higher level of inflammatory status may cause higher mortality in ventilated COVID-19 patients.

Our results showed that PP improved oxygenation in our COVID-19 patients with severe ARDS. There was a trend of improved oxygenation which was associated with a reduction in mortality, although without statistical significance. Our results may provide insights into the use of PP, including the timing of PP initiation, duration of PP, and predictors of successful resumption of the supine position.

### *4.1. Timing of PP initiation*

The early initiation of PP has been shown to improve short-term and longer-term mortality in non-COVID ARDS patients, while application later in the illness may limit the benefits.[14] We found that the time delay from the onset of severe ARDS to the start of PP was correlated with the need for a second session of PP, which has not been reported previously.[28–30] The later PP is started, the more likely that a second session will be needed. Further studies are needed to verify this observation.

### *4.2. Duration of PP*

The optimal duration of PP has not been confirmed. In the ProSEVA trial,[7] the duration of PP per session was $17 \pm 3$ hours. Another meta-analysis[6] reported that PP could reduce mortality in non-COVID patients with severe ARDS if PP was maintained for at least 12 hours a day.

In our patients, it usually failed to maintain PF ratio > 150 after turning them to supine position of patients who received prone positioning for 16–20 hours. Douglas WW et al. proposed that prolonged prone position was as safe as usual care,[31] therefore, we kept our patients on the prone position for a longer time. The mean duration of the first session of PP in the survivors was 54.8 hours. We found that the ICU mortality rate was inversely correlated with the improvement in P/F ratio and the reduction in driving pressure on the second day of the first PP session.

### *4.3. Predictors of successful resumption of the supine position*

Before the COVID-19 pandemic, severe ARDS patients received PP for 16–20 hours a day at our hospital. During the COVID-19 pandemic, we recognized that our routine practice should be changed due to the risk of frequently changing the patient's position. Prolonged PP has been a compromise; however the optimal duration of PP remains uncertain.

Guérin et al. reported that a PP session could be terminated if the patient's condition met the following criteria: P/F ratio $\geq$ 150 mmHg with PEEP $\leq$ 10 $cmH_2O$ and $FiO_2 \leq 0.6$ after resuming the supine position for at least 4 hours.[7] Based on these criteria, Douglas et al.[31] reported a 73.8% success rate of maintaining the supine position after one PP session in COVID-19 survivors. In our analysis, we identified three predictors that could best distinguish which patients would meet Guérin et al.'s criteria:[7] reduction in Pdrive at the first hour after PP, lower tidal volume at the fourth hour after PP, and improvement in P/F ratio on the second day after PP.

### *4.4. Respiratory mechanics*

Pdrive is calculated as the difference between Pplat and PEEP level.[32] Higher Pdrive has been correlated with higher mortality in non-COVID ARDS patients,[33] and lower Pdrive may also be related to lower mortality in COVID-19 ARDS patients.[34] In our patients, there was a trend of better survival in those whose Pdrive decreased after PP. Further studies are needed to validate these findings.

### *4.5. Limitations*

There were several limitations to this study. The most important is that this was a single-center study, and thus only a limited number of participants could be enrolled. Second, this was a retrospective study, and some data were missing. Third, we did not analyze differences in treatment modality, which may have influenced the outcomes. Although we have a standardized treatment strategy at our institute for severe COVID-19 patients, differences in treatment often occur in critical care, including ventilator settings, PEEP selection, and medications.

## 5. Conclusion

PP is feasible for COVID-19 patients with severe ARDS. The improvement in P/F ratio and reduction in Pdrive on the second day after PP were correlated with a reduction in mortality. Three parameters could predict successful resumption of the supine position, however further investigations are needed to verify our findings.

## Funding

None.

## Conflicts of interest

The authors report no conflicts of interest for this work.

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