Original Article

PaO_2 / FiO_2 ratio responsiveness to prone positioning in intubated patients with severe COVID-19: a retrospective observational study

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Aim: Prone positioning of coronavirus disease 2019 (COVID-19) patients could improve oxygenation. However, clinical data on prone positioning of intubated COVID-19 patients are limited. We investigated trends of PaO_2 / FiO_2 ratio values in patients during prone positioning to identify a predictive factor for early detection of patients requiring advanced therapeutic intervention such as extracorporeal membrane oxygenation (ECMO).

Methods: This retrospective, observational cohort study was undertaken between April 2020 and May 2021 in a tertiary referral hospital for COVID-19 in Osaka, Japan. We included intubated adult COVID-19 patients treated with prone positioning within the first 72 h of admission to the intensive care unit and followed them until hospital discharge or death. Primary outcomes were in-hospital mortality and escalation of care to ECMO. We used unsupervised k-means clustering modeling to categorize COVID-19 patients by PaO_2 / FiO_2 ratio responsiveness to prone positioning.

Results: The final study cohort comprised 54 of 155 consecutive severe COVID-19 patients. Three clusters were generated according to trends in PaO_2 / FiO_2 ratios during prone positioning (cluster A, n = 16; cluster B, n = 24; cluster C, n = 14). Baseline characteristics of all clusters were almost similar. Cluster A (no increase in PaO_2 / FiO_2 ratio during prone positioning) had a significantly higher proportion of patients placed on ECMO or who died (6/16, 37.5%). Numbers of patients with ECMO and with in-hospital death were significantly different between the three groups ($p = 0.017$).

Conclusion: In Japanese patients intubated due to COVID-19, clinicians should consider earlier escalation of treatment, such as facility transfer or ECMO, if the PaO_2 / FiO_2 ratio does not increase during initial prone positioning.

Key words: Acute respiratory distress syndrome, COVID-19, ECMO, PaO_2 / FiO_2 ratio, prone positioning

INTRODUCTION

SEVERE ACUTE RESPIRATORY syndrome coronavirus 2 (SARS-CoV-2) was discovered at the end of 2019 and has developed into a global pandemic resulting in more than 5 million deaths.[1] It has been reported that among patients suffering from coronavirus disease 2019 (COVID-19), a significant proportion develop acute respiratory distress syndrome (ARDS), with 14–17% of the hospitalized patients with COVID-19 requiring mechanical ventilation and approximately half of them dying.[2–4] Despite the large number of deaths, there is still much debate about the treatment of COVID-19, and particularly, treatment options for patients with severe COVID-19 are limited.[5,6]

In patients with moderate to severe ARDS, excluding COVID-19, prone positioning has been shown to improve the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO_2 / FiO_2 ratio)[7] and reduce mortality.[8,9] Furthermore, there are increasing reports of prone positioning being effective and improving the PaO_2 / FiO_2

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ratio in patients with severe COVID-19.[10–12] However, expecting too much benefit from prone positioning and repeating it several times can lead to delays in the expansion of advanced therapy, such as missing the appropriate time to introduce extracorporeal membrane oxygenation (ECMO), despite some studies indicating that early introduction of ECMO might improve outcomes.[13–16]

Thus, the aim of this study was to investigate the evolution of the PaO_2 / FiO_2 ratio in patients treated with prone positioning and to identify methods for early detection of cases requiring further therapeutic intervention, such as the introduction of ECMO.

METHODS

Design and setting

THIS RETROSPECTIVE, OBSERVATIONAL cohort study was undertaken in a single center, Osaka Medical and Pharmaceutical University Hospital (Osaka, Japan) between April 2020 and May 2021. We included consecutive intubated adult patients with COVID-19 in whom prone positioning was carried out within the first 72 h of intensive care unit (ICU) admission. We excluded patients who were intubated and were placed in the prone position at another hospital before admission or who were placed in the prone positioning after reintubation.

The study, which followed the principles of the Declaration of Helsinki, was approved by the Institutional Review Board of the Osaka Medical and Pharmaceutical University (approval number: #2021–152). Because of the retrospective nature of the study, the requirement for informed consent was waived.

Management of prone positioning and extracorporeal membrane oxygenation

Intubated COVID-19 patients were principally placed in prone positioning when their PaO_2 / FiO_2 ratio decreased to less than 200 mmHg. Prone positioning was maintained for approximately 16 h. The next day, the patient was again placed in prone positioning if the PaO_2 / FiO_2 ratio decreased to below 200 after returning to supine positioning. Prone positioning was terminated if the PaO_2 / FiO_2 ratio remained above 200 mmHg in the supine position or it had been used three times. Those patients whose PaO_2 / FiO_2 ratio remained below 100 mmHg or who had an arterial blood pH less than 7.25 with a $PaCO_2$ of more than 60 mmHg, despite adjustment of ventilator settings, were considered to be eligible for ECMO introduction.

Data collection

Patient characteristics such as age, sex, body mass index, smoking, days from symptoms onset, and respiratory mechanics were collected, as were pre-existing conditions including hypertension, diabetes, dyslipidemia, pulmonary disease, and chronic kidney disease. Changes in arterial blood gases and ventilator settings before and after first prone positioning were recorded and calculated as the PaO_2 / FiO_2 ratio (ratio between the partial pressure of oxygen, PaO_2, and inspired fraction of oxygen, FiO_2). Furthermore, we calculated the mean of the PaO_2 / FiO_2 ratio at three different time points: before, during, and within 10 h after prone positioning in each patient. In our ICU, arterial blood gases were recorded approximately every 4 h.

Outcomes

The primary outcome was set as in-hospital mortality and/or escalation of care to ECMO. The secondary outcomes were tracheostomy. Each patient was followed until hospital discharge or death.

Statistical analysis

Descriptive statistics were calculated as median (range) or number (proportion), as appropriate. Univariate differences between groups were assessed using the Mann–Whitney *U*-test, Kruskal–Wallis test, χ^2-test, or Fisher's exact test, as appropriate.

To phenotype the COVID-19 patients by PaO_2 / FiO_2 ratio responsiveness to prone positioning, a time-series dataset of PaO_2 / FiO_2 ratio transitions was analyzed and categorized using k-means clustering. K-means clustering is a technique that aims to divide N observations into K clusters. Each observation belongs to the cluster with the closest mean that serves as the cluster prototype. As the result of unsupervised clustering, all patients were categorized into three clusters. The optimal number of clusters was determined by the size of the clusters and clinical interpretability evaluated by the characteristics of the patient baseline characteristics of COVID-19 in each cluster.

All statistical inferences were carried out with a two-sided test at a 5% significance level. All analyses were performed using STATA MP software version 17 (Stata Corp.) and JMP software version 15.0 (SAS Institute).

RESULTS

THE PATIENT FLOW diagram in this study is shown in Figure 1. Between April 2020 and May 2021, 155 adult

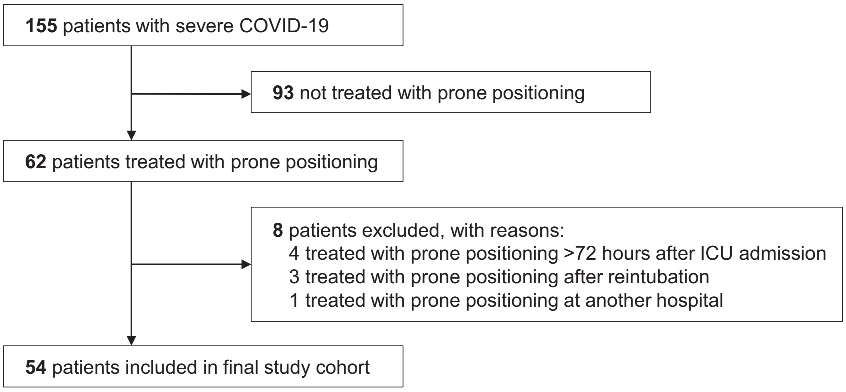

Fig. 1. Patient flow diagram of intubated patients with severe coronavirus disease 2019 (COVID-19). ICU, intensive care unit.

intubated patients with COVID-19 were admitted to our ICU. Among them, 62 were placed in the prone position. After excluding eight patients who met at least one exclusion criterion, we analyzed 54 patients as the final study cohort. The baseline patient demographic and clinical characteristics are summarized in Table 1. The median age was 66 (35–89) years, most patients were male (75.9%), and the median body mass index was 26 (16.8–45.7) kg/m^2.

The trend in PaO_2 / FiO_2 ratios before, during, and after prone positioning is illustrated in Figure 2. Using the unsupervised k-means clustering model, three patient clusters were generated according to the trend in PaO_2 / FiO_2 ratios during prone positioning. Cluster A included 16 patients, cluster B included 24 patients, and cluster C included 14 patients. In comparison to the baseline PaO_2 / FiO_2 ratio value, Cluster A contained the patients in whom the PaO_2 / FiO_2 ratio did not increase during prone positioning. Cluster B contained the patients in whom the PaO_2 / FiO_2 ratio increased during prone positioning but returned to baseline after the patients were returned to the supine position. Cluster C contained the patients in whom the PaO_2 / FiO_2 ratio increased during prone positioning and

Table 1. Baseline characteristics of intubated patients with severe COVID-19, grouped according to PaO_2 / FiO_2 ratio responsiveness to prone positioning

	Overall (n = 54)	Cluster A (n = 16)	Cluster B (n = 24)	Cluster C (n = 14)	p value
Age, years	66 (35–89)	61 (37–79)	65 (35–79)	66 (54–89)	0.492
Male	41 (75.9)	13 (81.3)	18 (75.0)	10 (71.4)	0.813
Body mass index, kg/m^2	26 (16.8–45.7)	27.5 (16.8–45.7)	25.5 (20.4–36.4)	25.0 (20.6–30.2)	0.066
Time from symptom onset (days)	9 (0–35)	9 (0–24)	9.5 (1–35)	9 (4–13)	0.686
Current smoker	10 (18.5)	3 (18.8)	4 (16.7)	3 (21.4)	0.964
Pre-existing conditions					
Hypertension	33 (61.1)	3 (18.8)	19 (79.2)	11 (78.6)	<0.01
Diabetes mellites	16 (29.6)	3 (18.8)	8 (33.3)	5 (35.7)	0.518
Dyslipidemia	15 (27.8)	1 (6.3)	8 (33.3)	6 (42.9)	0.059
Pulmonary disease	7 (13.0)	3 (18.8)	4 (16.7)	0 (0.0)	0.240
Chronic kidney disease	2 (3.7)	0 (0.0)	1 (4.2)	0 (0.0)	0.529
PEEP, cmH_2O	11 (8–18)	10.0 (8.0–18.0)	11.5 (10.0–15.0)	11.0 (8.0–16.0)	0.982
PaO_2 / FiO_2 ratio, mmHg	125 (72–221)	109 (72–190)	136 (79–187)	147 (104–221)	0.019

Data are expressed either as median (range) or as frequency (percentage). Cluster A, PaO_2 / FiO_2 ratio did not increase during prone positioning; Cluster B, PaO_2 / FiO_2 ratio increased during prone positioning but returned to baseline after patients were returned to supine position; Cluster C, PaO_2 / FiO_2 ratio increased during prone positioning and remained elevated after patients were returned to the supine position.
Abbreviation: PEEP, positive end-expiratory pressure.

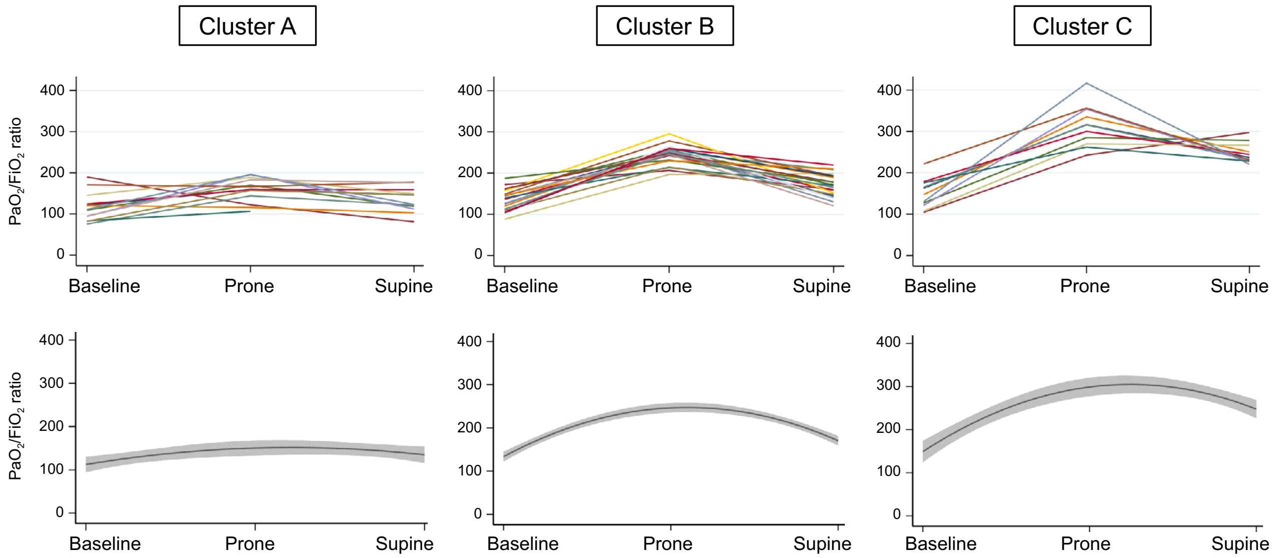

Fig. 2. Time trend in PaO_2 / FiO_2 ratios before, during, and after prone positioning in intubated patients with severe coronavirus disease 2019 (COVID-19). All 54 patients with COVID-19 were categorized into three clusters by PaO_2 / FiO_2 ratio responsiveness to prone positioning using unsupervised k-means clustering. Each of the lower panels shows a nonlinear graph and the 95% confidence interval (gray highlight). Cluster A, PaO_2 / FiO_2 ratio did not increase during prone positioning; Cluster B, PaO_2 / FiO_2 ratio increased during prone positioning but returned to baseline after patients were returned to supine position; Cluster C, PaO_2 / FiO_2 ratio increased during prone positioning and remained elevated after patients were returned to the supine position.

remained elevated after the patients were returned to the supine position.

The patient demographic and clinical characteristics for each cluster are summarized in Table 1. Sex and median ages were similar between the three clusters. Body mass index was slightly different between clusters A, B, and C (27.5 [16.8–45.7] kg/m^2, 25.5 [20.4–36.4] kg/m^2, and 25.0 [20.6–30.2] kg/m^2, respectively; $p = 0.066$). There were also no significant differences between the three clusters in median days since onset of symptoms and median positive airway pressure before first prone positioning.

Outcome assessment is shown in Table 2. No patients in cluster C were placed on ECMO or died. In contrast, cluster A had a significantly higher proportion of patients who were placed on ECMO or who died than cluster C (6/16 versus 0/14, $p = 0.019$). In addition, the total numbers of patients treated with ECMO and patients who died in hospital were significantly different between the three groups ($p = 0.017$). Tracheostomy was carried out in 7 of the 16 (43.8%) patients in cluster A, 9 of 24 (37.5%) in cluster B, and 4 of 14 (23.6%) in cluster C ($p = 0.690$).

Table 2. Outcome measures in intubated patients with severe COVID-19, grouped according to PaO_2 / FiO_2 ratio responsiveness to prone positioning

	Cluster A (n = 16)	Cluster B (n = 24)	Cluster C (n = 14)	p value
ECMO or in-hospital mortality	6 (37.5)	3 (12.5)	0 (0.0)	0.017
In-hospital mortality	3 (18.8)	2 (8.3)	0 (0.0)	0.205
ECMO	3 (18.8)	1 (4.2)	0 (0.0)	0.106
Tracheostomy	7 (43.8)	9 (37.5)	4 (23.6)	0.690

Data are expressed as frequency (percentage). Cluster A, PaO_2 / FiO_2 ratio did not increase during prone positioning; Cluster B, PaO_2 / FiO_2 ratio increased during prone positioning but returned to baseline after patients were returned to supine position; Cluster C, PaO_2 / FiO_2 ratio increased during prone positioning and remained elevated after patients were returned to the supine position.
Abbreviation: ECMO, extracorporeal membrane oxygenation.

DISCUSSION

IN THIS RETROSPECTIVE cohort study of intubated COVID-19 patients, we identified the patient group in which the PaO_2 / FiO_2 ratio did not increase during prone positioning as having a significantly higher proportion of patients who were placed on ECMO or who died. It is clinically important to determine whether a patient is eligible for ECMO early after deterioration because several reports have shown that delayed introduction of ECMO leads to a poor prognosis.[13,14] Therefore, in this study, we considered the patients in whom ECMO was introduced to be equivalent to those who died without receiving ECMO and set the primary outcome as a composite outcome containing both mortality and escalation to ECMO. The findings in this study indicate that clinicians should consider the expansion of advanced treatments such as ECMO in patients in whom the PaO_2 / FiO_2 ratio does not increase during initial prone positioning (Fig. S1).

The main mechanisms to improve oxygenation appear to be improving ventilation–perfusion matching and reducing alveolar shunt, which result in improved gas exchange.[10,12,17] A more homogenous distribution of ventilation is reported to reduce the risk of ventilator-induced lung injury.[18,19] Furthermore, the reduction in respiratory rate observed during awake prone positioning might indicate a reduction in respiratory drive and fluctuations of transpulmonary pressure, resulting in fewer instances of patient self-inflicted lung injury.

The PROFLO study[20] previously indicated that awake prone positioning in nonintubated patients with COVID-19 did not reduce the rate of intubation. However, a recent randomized controlled trial[21] showed that awake prone positioning of nonintubated patients with COVID-19 reduced the need for intubation without adverse events. This could lead to a trend in favor of awake prone therapy in the future. In intubated patients with COVID-19, several studies have shown that oxygenation was improved by prone positioning. There are few reports and limited data on prone positioning in intubated patients with COVID-19. To our knowledge, this is the first report to conduct treatment in intubated patients with COVID-19 using PaO_2 / FiO_2 ratio responsiveness during prone positioning as an indicator of patient outcome.

A clinically relevant finding from this study was that the subsequent treatment can be estimated from the trend of the PaO_2 / FiO_2 ratio during initial prone positioning. Other factors that could predict the patients at high risk of death or conversion to ECMO treatment include blood test data such as lactate dehydrogenase, D-dimer, high-sensitivity cardiac troponin I, interleukin-6, or ferritin[22–25] and computed tomography (CT) findings. Indeed, the distribution of pneumonia or the presence of dorsal atelectasis on CT images could be associated with disease severity in patients with COVID-19.[26,27] However, in clinical settings it is difficult to move critically ill patients to undertake CT scanning, and thus, frequent monitoring with CT scanning is not practical. The trend in the PaO_2 / FiO_2 ratio is considered more useful because it is simple and can be captured visually as a bedside monitoring tool.

We acknowledge several limitations in our study. First, the sample size was relatively small. Second, the nature of a single-center, retrospective, observational study was a concern. These limitations could limit the generalizability of the main findings in this study. Finally, some PaO_2 / FiO_2 ratio data before and after prone positioning were missing for some patients who we placed in the prone position immediately after intubation or in whom we introduced ECMO as soon as we found prone positioning to be ineffective. Therefore, we took the missing values into account and created a separate set of the three clusters, nonlinear graphs, and 95% confidence intervals. Because the graphs were almost identical compared with those in which the missing values were not considered, we considered this issue to be of little importance in most cases.

CONCLUSION

AMONG ADULT JAPANESE patients with severe COVID-19, clinicians should consider earlier escalation of advanced treatment, such as facility transfer or introduction of ECMO, if the PaO_2 / FiO_2 ratio does not increase during initial prone positioning.

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DISCLOSURE

APPROVAL OF THE research protocol with approval no. and committee name: This study was approved by the Institutional Review Board of the Osaka Medical and Pharmaceutical University (approval number: #2021–152).

Informed consent: N/A.

Registry and registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Visual abstract. COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.