Lower Driving Pressure and Neuromuscular Blocker Use Are Associated With Decreased Mortality in Patients With COVID-19 ARDS

Bo Young Lee, Song-I Lee, Moon Seong Baek, Ae-Rin Baek, Yong Sub Na, Jin Hyoung Kim, Gil Myeong Seong, and Won-Young Kim

BACKGROUND: The impact of mechanical ventilation parameters and management on outcomes of patients with coronavirus disease 2019 (COVID-19) ARDS is unclear. METHODS: This multicenter observational study enrolled consecutive mechanically ventilated patients with COVID-19 ARDS admitted to one of 7 Korean ICUs between February 1, 2020–February 28, 2021. Patients who were age < 17 y or had missing ventilation parameters for the first 4 d of mechanical ventilation were excluded. Multivariate logistic regression was used to identify which strategies or ventilation parameters that were independently associated with ICU mortality. RESULTS: Overall, 129 subjects (males, 60%) with a median (interquartile range) age of 69 (62–78) y were included. Neuromuscular blocker (NMB) use and prone positioning were applied to 76% and 16% of subjects, respectively. The ICU mortality rate was 37%. In the multivariate analysis, higher dynamic driving pressure (ΔP) values during the first 4 d of mechanical ventilation were associated with increased mortality (adjusted odds ratio 1.16 [95% CI 1.00–1.33], $P = .046$). NMB use was associated with decreased mortality (adjusted odds ratio 0.27 [95% CI 0.09–0.81], $P = .02$). The median tidal volume values during the first 4 d of mechanical ventilation and the ICU mortality rate were significantly lower in the NMB group than in the no NMB group. However, subjects who received NMB for ≥ 6 d (vs < 6 d) had higher ICU mortality rate. CONCLUSIONS: In subjects with COVID-19 ARDS receiving mechanical ventilation, ΔP during the first 4 d of mechanical ventilation was independently associated with mortality. The short-term use of NMB facilitated lung-protective ventilation and was independently associated with decreased mortality. *Key words: COVID-19; driving pressure; mechanical ventilation; neuromuscular blockade; respiratory distress syndrome; SARS-CoV-2.* [Respir Care 2022;67(2):216–226. © 2022 Daedalus Enterprises]

Introduction

As of August 21, 2021, over 209 million confirmed cases of coronavirus disease 2019 (COVID-19) have been reported worldwide, and over 4 million related deaths have been confirmed (https://www.who.int/emergencies/diseases/novel-coronavirus-2019. *Accessed August 21, 2021*). Many of those who were hospitalized for COVID-19 have received mechanical ventilation due to severe pneumonia and ARDS.[1,2] ARDS is characterized by the acute onset of noncardiogenic pulmonary edema and hypoxemia that could be aggravated by ventilator-induced lung injury.[3] The mortality of patients with severe COVID-19 admitted to the ICU is high, ranging from 15–74%.[4,5]

Early reports demonstrated that COVID-19 ARDS may have a different physiology and can be categorized into 2 subphenotypes according to respiratory mechanics: "early" ARDS with high compliance and low recruitability and "late" ARDS with low compliance and high recruitability.[6,7] Thus, the applicability of current evidence-based ARDS management, such as low tidal volume (V_T), PEEP, and prone positioning, for patients with COVID-19 ARDS is controversial. Although numerous studies have described ventilation parameters and strategies in mechanically ventilated patients with COVID-19,[8] their potential impact on patient outcomes is unclear. For instance, although neuromuscular blockers (NMBs) and prone positioning have been extensively studied in subjects with non-COVID-19 ARDS,[9,10] studies on their impact on mortality of patients with COVID-19 are limited.

Therefore, this study aimed to investigate the mechanical ventilation settings and management strategies independently associated with ICU mortality in subjects with COVID-19 ARDS.

Methods

Setting and Subjects

The Korean study group on the oxygenated or ventilated subjects with severe COVID-19 (KOVIDS) is a multi-center, observational cohort study that enrolled adult (≥ 17 y old) subjects with COVID-19 who were admitted to one of the ICUs at the 7 tertiary or referral hospitals in South Korea. The institutional review boards (IRBs) of the participating hospitals approved the study protocol, and the need for informed consent was waived due to the observational nature of the study (IRB of Chung-Ang University Hospital, No. 2103–009-19360). Subjects' electronic medical records were reviewed by intensivists or research nurses trained in critical care, collecting de-identified subject data on demographics, comorbidities, dates of first symptom and COVID-19 diagnosis, oxygen support devices (nasal cannula, oxygen mask, high-flow nasal cannula, or mechanical ventilation), in-hospital medications and procedures, vital signs, laboratory and microbiological data, and outcomes according to a standardized case record form. Each investigator added the data collected from this form to an online database (Google Sheets, Google, Mountain View, California). Two independent investigators (WYK and MSB) screened the database for errors and verified data by visual inspection of distribution plots. Local investigators were contacted for any queries; then validated data were entered into the final database. The recommendations from the Surviving Sepsis Campaign guidelines for critically ill adults with COVID-19, including standard management of ARDS, were followed in all hospitals.[11] PEEP/F_{IO_2} titration was not standardized but was left at the discretion of the attending physician. This study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

QUICK LOOK

Current knowledge

Given the recent controversy concerning differences in physiology between coronavirus disease 2019 (COVID-19) and non-COVID-19 ARDS, numerous studies have described ventilation parameters and management in patients with COVID-19. However, there are limited data on the potential impact on mortality.

What this paper contributes to our knowledge

Higher dynamic driving pressure, peak inspiratory pressure, and mechanical power values during the first 4 d of mechanical ventilation were independently associated with ICU mortality in subjects with COVID-19 ARDS. PEEP, tidal volume, compliance, and ventilatory ratio were not. In subjects who received a neuromuscular blocker, tidal volume values during the first 4 d of mechanical ventilation and ICU mortality rate were significantly lower. Prone positioning was not significantly associated with decreased mortality.

For the current study, all consecutive subjects with COVID-19 registered in the data set between February 1, 2020–February 28, 2021 in whom mechanical ventilation was applied for ARDS were included. Patients were excluded if they were age < 17 y, were not intubated, did not meet the diagnostic criteria for ARDS, had a do-not-intubate order, or had missing ventilation parameter values during the first 4 d of mechanical ventilation. The subjects were followed until hospital discharge, death, or June 17, 2021, which was the date of last chart review. Survival status in the 60 d following hospital admission was determined for all subjects.

Data Collection and Definitions

Baseline data collected at hospital admission included age, sex, body mass index, smoking status, comorbidities,

Dr Bo Young Lee is affiliated with Division of Allergy and Respiratory Diseases, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea. Dr Song-I Lee is affiliated with Department of Pulmonary and Critical Care Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea. Drs Moon Seong Baek and Won-Young Kim are affiliated with Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea. Dr Baek is affiliated with Division of Allergy and Pulmonology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea. Dr Na is affiliated with Department of Pulmonology and Critical Care Medicine, Chosun University Hospital, Gwangju, Republic of Korea. Dr Jin Hyoung Kim is affiliated with Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea. Dr Seong is affiliated with Department of Internal Medicine, Jeju National University College of Medicine, Jeju, Republic of Korea.

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Correspondence: Won-Young Kim MD PhD, Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Republic of Korea. E-mail: wykim81@cau.ac.kr.

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date of first symptom, date of hospital admission, and laboratory findings. In-hospital admission data included the date of mechanical ventilation initiation, corticosteroid, and rescue therapies for ARDS (NMB, prone positioning, and extracorporeal membrane oxygenation [ECMO]). The severity of ARDS, Sequential Organ Failure Assessment (SOFA) score,[12] and arterial blood gas data at the time of mechanical ventilation initiation were recorded. We also collected the daily mean values of the following ventilation parameters for the first 4 d of mechanical ventilation, with day 1 indicating the first day of intubation: breathing frequency, V_T, PEEP, and peak inspiratory pressure (PIP). The parameters measured before mechanical ventilation optimization were not included.

Laboratory confirmation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was based on a positive result according to a real-time reverse transcription polymerase chain reaction assay from upper respiratory tract specimens.[13] Immunosuppression was identified when the subject had malignancy, organ transplant, or immunosuppressive medications. ARDS was defined based on the Berlin criteria and classified into mild (P_{aO_2}/F_{IO_2} 200–300 mm Hg), moderate (P_{aO_2}/F_{IO_2} 100–200 mm Hg), and severe ($P_{aO_2}/F_{IO_2} \leq 100$ mm Hg).[14] The use of NMB was defined as continuous administration within 24 h after intubation to facilitate mechanical ventilation or prone positioning. Prone positioning was defined as any episode of proning initiated within the first 2 d of mechanical ventilation. V_T was expressed in mL/kg ideal body weight (IBW). Dynamic driving pressure (ΔP) was calculated as PIP, PEEP, and dynamic compliance as $V_T/\Delta P$.[15] We used dynamic ΔP because plateau pressure was not measured for subjects who received pressure-control continuous mandatory ventilation. Mechanical power was defined as $0.098 \times V_T \times$ breathing frequency $\times$ (PIP $1/2 \times \Delta P$).[16] Ventilatory ratio was calculated as (minute ventilation $\times P_{aCO_2}$)/(IBW $\times$ 100 $\times$ 37.5).[17]

Outcome Measures

The primary outcome measure was ICU mortality. The secondary outcome measures were (1) ventilator weaning, defined as freedom from mechanical ventilation for $\geq$ 48 h; (2) ventilator-free days at day 28, defined as the number of d that the subject was alive and free from mechanical ventilation within 28 d after intubation; (3) hospital length of stay; (4) tracheostomy; (5) renal replacement therapy during ICU stay; (6) superinfection; and (7) hospital, 28-d, and 60-d mortality.

Statistical Analysis

Data were reported as the median (interquartile range [IQR]) or the mean $\pm$ SD for continuous variables and as the number (percentage) for categorical variables. Continuous variables were compared using Mann-Whitney *U* test, whereas categorical variables were compared using the chi-square test or Fisher exact test. Continuous variables were compared among more than 2 groups with the Kruskal-Wallis test. Ventilation parameters during the first 4 d of mechanical ventilation were described by line graphs. Kaplan-Meier survival curves until day 60 were generated and compared between groups using log-rank tests.

Multivariate logistic regression was performed to quantify the association of mechanical ventilation settings and ventilation management with ICU mortality, with adjustment for other covariates. Independent variables were selected among variables with *P* values of $< .10$ in the univariate analysis and potential confounders that were judged based on clinical expertise. The national health system was extremely pressured during the third wave of the epidemic in Korea (December 2020–January 2021). Therefore, the potential effect of changes in the treatment period was assessed by including hospital admission date (November 30, 2020, and earlier vs December 1, 2020, and later) in the model. For ventilation parameters, the mean values from the first 4 d of mechanical ventilation were considered in the model. As serum creatinine showed a high collinearity with the SOFA score at the start of mechanical ventilation, serum creatinine was excluded in the final model because it was already included in the SOFA renal subscore. Similarly, PEEP, PIP, ΔP, and mechanical power showed high collinearity (Table S1, see supplementary material related to this paper at http://rc.rcjournal.com), but only ΔP was included in the final model because previous studies demonstrated that ΔP is the optimal ventilation parameter for stratifying the risk of death among subjects with ARDS receiving mechanical ventilation.[18,19] After undergoing final assessment, a multivariate model was constructed using stepwise backward selection. The model's discrimination was assessed with C statistic ($c = 0.82$), and its calibration was assessed with Hosmer-Lemeshow test (chi-square = 4.93, $P = .77$). To assess the possible association of PEEP, PIP, and mechanical power with ICU mortality, we performed a secondary multivariate analysis replacing ΔP by those variables.

No imputation strategy was conducted because only few variables had missing data (13/5,516, 0.2%). There were no missing values for ventilation parameters. All statistical analyses were performed using IBM SPSS software (version 26.0; IBM, Armonk, New York). A 2-sided *P* value of $< .05$ was considered statistically significant.

Results

Subject Characteristics

Among the 1,575 patients evaluated for eligibility (Fig. 1), 1,446 patients were excluded due to no oxygen support ($n = 1,077$), conventional oxygen therapy only ($n = 184$), high-flow nasal cannula only ($n = 138$), and a do-not-

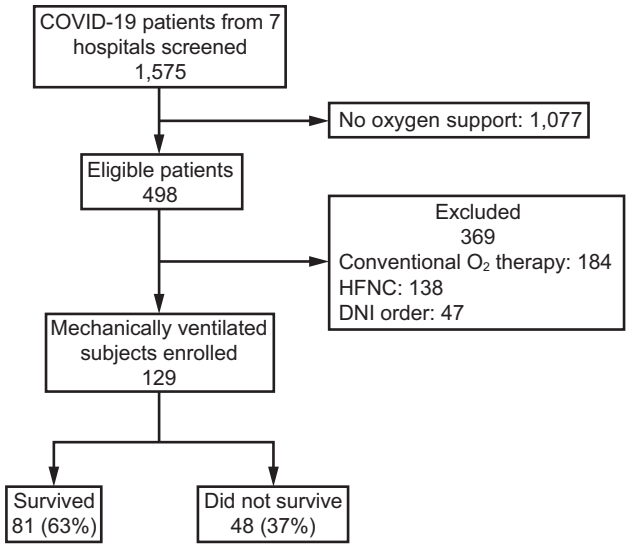

Figure 1. Flow chart. HFNC = high-flow nasal cannula. DNI = do not intubate.

intubate order ($n = 47$). Finally, 129 mechanically ventilated subjects were included in the study, and all met the criteria for ARDS. The median duration of follow-up was 27 d (IQR 20–44 d). The baseline subject characteristics are shown in Table 1. The median age, body mass index, and SOFA score at the start of mechanical ventilation were 69 y (IQR 62–78 y), 25.3 kg/m^2 (IQR 22.5–27.8 kg/m^2), and 9 (IQR 8–11), respectively. In total, 60% and 18% of the subjects were male and ever smokers, respectively. The most frequent comorbidities were hypertension (60%) and diabetes (41%). The median time from symptom onset to hospital admission was 5 d (IQR 2–9 d). Corticosteroid was used in 92%, NMB in 76%, prone positioning in 16%, and ECMO in 16%. ICU nonsurvivors were older, had higher SOFA score at the start of mechanical ventilation, had lower NMB use, and had lower pH and serum bicarbonate at the start of mechanical ventilation. There was no significant difference in the median time from symptom onset to hospital admission between survivors and nonsurvivors.

Overall, 19%, 43%, and 38% of subjects had mild, moderate, and severe ARDS on day 1 of mechanical ventilation, respectively (Table S2, see supplementary material related to this paper at http://rc.rcjournal.com). The median SOFA score at the start of mechanical ventilation was higher in subjects with severe ARDS. However, the degree of ARDS severity was not associated with significant differences in the use of corticosteroids, NMB, prone positioning, or ECMO.

Ventilation Parameters

The median time from hospital admission to mechanical ventilation initiation was 1 d (IQR 0–3 d), with no significant difference between survivors and nonsurvivors (Table 1). All subjects received pressure- or volume-control continuous mandatory ventilation. On day 1 of mechanical ventilation, the median V_T, PEEP, PIP, ΔP, and mechanical power were 6.9 mL/kg IBW (IQR 6.2–8.1 mL/kg IBW), 10 cm H_2O (IQR 9–12 cm H_2O), 24 cm H_2O (IQR 21–28 cm H_2O), 14 cm H_2O (IQR 11–16 cm H_2O), and 26.0 J/min (IQR 21.3–32.5 J/min), respectively (Table 1). Distributions of the median V_T and PEEP were similar between survivors and nonsurvivors, but the median PIP, ΔP, and mechanical power were significantly higher in nonsurvivors than in survivors. In addition, the median compliance was lower and median ventilatory ratio was higher in nonsurvivors than in survivors. However, these findings did not reach statistical significance. The ventilation strategies (V_T and PEEP) did not vary with the degree of ARDS severity (Table S2, see supplementary material related to this paper at http://rc.rcjournal.com). However, the median PIP, ΔP, mechanical power, and ventilatory ratio increased with the severity of ARDS.

During the first 4 d of mechanical ventilation, the median V_T values of 6.8–7.3 mL/kg IBW were maintained in both survivors and nonsurvivors (Fig. 2). The differences in the median PEEP between survivors and nonsurvivors were not clinically relevant, although statistically significant differences were observed on day 3 and day 4 of mechanical ventilation. The median PIP and ΔP values were significantly higher in nonsurvivors than in survivors, despite both groups receiving median PIP values of < 25 cm H_2O and median ΔP values of < 15 cm H_2O. The median compliance values were significantly lower in nonsurvivors on day 3 and day 4. The median mechanical power values were significantly higher in nonsurvivors during the first 4 d of mechanical ventilation.

Clinical Outcomes

The rates of ICU mortality, ventilator weaning, and superinfection were 37%, 60%, and 53%, respectively. The median ventilator-free d at day 28 was 8.2 ± 9.7 d, and the median hospital length of stay was 27 d (IQR 20–44 d). Tracheostomy was performed in 33%, and 25% received renal replacement therapy during their ICU stay. The ICU mortality rates were 20% in mild, 40% in moderate, and 43% in severe ARDS ($P = .13$) (Table S2, see supplementary material related to this paper at http://rc.rcjournal.com). Other study outcomes were not generally affected by the degree of ARDS severity, except for the highest superinfection rate in subjects with severe ARDS.

Association of Ventilation Parameters and Management With ICU Mortality

After adjustment for confounding factors, the independent predictors of ICU mortality were a higher age

Table 1. Baseline Characteristics of Subjects According to ICU Survival Status

	All ($N = 129$)	Survivors ($n = 81$)	Nonsurvivors ($n = 48$)	P
Age, y	69 (62–78)	65 (61–74)	76 (69–81)	< .001
Male sex	77 (60)	50 (62)	27 (56)	.54
Body mass index, kg/m^2	25.3 (22.5–27.8)	25.3 (22.3–27.3)	26.0 (22.6–28.7)	.26
Ever smoker	23 (18)	14 (17)	9 (19)	.83
Date of hospital admission				.33
November 30 and earlier	61 (47)	41 (51)	20 (42)	
December 1 and later	68 (53)	40 (49)	28 (58)	
Comorbidities				
Hypertension	77 (60)	50 (62)	27 (56)	.54
Diabetes	53 (41)	32 (40)	21 (44)	.64
Cerebrovascular accident	8 (6)	4 (5)	4 (8)	.47
COPD	6 (5)	2 (3)	4 (8)	.19
Dialysis	10 (8)	5 (6)	5 (10)	.50
Immunosuppression	10 (8)	5 (6)	5 (10)	.50
Symptom onset, hospital admission, d	5 (2–9)	6 (3–9)	4 (1–7)	.07
Hospital admission, mechanical ventilation, d	1 (0–3)	1 (0–3)	1 (0–4)	.37
Severity of ARDS				.13
Mild	25 (19)	20 (25)	5 (10)	
Moderate	55 (43)	33 (41)	22 (46)	
Severe	49 (38)	28 (35)	21 (44)	
SOFA score at the start of mechanical ventilation	9 (8–11)	9 (7–11)	11 (8–13)	.001
Corticosteroid	119 (92)	74 (91)	45 (94)	.74
Neuromuscular blocker	98 (76)	68 (84)	30 (63)	.006
Duration, d	5 (4–9)	5 (4–8)	8 (4–15)	.008
Prone positioning	21 (16)	16 (20)	5 (10)	.17
ECMO	20 (16)	9 (11)	11 (23)	.07
Laboratory data at admission				
Lymphocyte, %	9.7 (5.0–19.0)	10.0 (5.8–18.2)	8.9 (4.8–19.5)	.53
Platelet count, 1,000/mm^3	181 (134–222)	187 (144–223)	160 (117–215)	.065
Creatinine, mg/dL	0.8 (0.7–1.2)	0.8 (0.6–1.0)	0.9 (0.7–1.5)	.068
Total bilirubin, mg/dL	0.5 (0.4–0.7)	0.5 (0.4–0.7)	0.5 (0.4–0.7)	.96
Mode of mechanical ventilation				.31
PC-CMV	65 (50)	38 (47)	27 (56)	
VC-CMV	64 (50)	43 (53)	21 (44)	
Ventilatory parameters				
Breathing frequency, breaths/min	21 (18–24)	21 (18–24)	20 (18–26)	.97
Tidal volume, mL/kg IBW	6.9 (6.2–8.1)	7.0 (6.2–7.9)	6.8 (6.2–8.3)	.59
Minute ventilation, L/min*	9.3 (7.7–10.4)	9.0 (7.7–10.2)	9.6 (7.8–10.5)	.23
PEEP, cm H_2O	10 (9–12)	10 (9–12)	10 (10–12)	.94
PIP, cm H_2O	24 (21–28)	23 (20–27)	25 (23–28)	.02
Dynamic driving pressure, cm H_2O†	14 (11–16)	12 (11–15)	14 (13–18)	.003
Dynamic compliance, mL/cm H_2O‡	30.4 (26.4–37.6)	33.2 (27.1–38.8)	29.2 (24.0–35.3)	.08
Mechanical power, J/min§	26.0 (21.3–32.5)	25.1 (19.0–31.4)	27.9 (23.8–32.7)	.03
Ventilatory ratio‖	1.6 (1.3–2.1)	1.6 (1.2–1.9)	1.8 (1.3–2.3)	.060
Blood gases at the start of mechanical ventilation				
P_{aO_2}/F_{IO_2}	117 (87–180)	123 (87–197)	109 (85–134)	.13

(Continued)

(adjusted odds ratio 1.10 [95% CI 1.04–1.15], $P = .001$) and a higher ΔP (adjusted odds ratio 1.16 [95% CI 1.00–1.33], $P = .046$) (Table 2). NMB use was associated with decreased mortality (adjusted odds ratio 0.27 [95% CI 0.09–0.81], $P = .02$). Prone positioning, V_T, compliance, and ventilatory ratio were not significantly associated with increased mortality. When ΔP was replaced by PEEP, PIP, or mechanical power, a higher age, no NMB use, a higher PIP, and a higher mechanical power were significantly associated with increased

Table 1. Continued

	All ($N = 129$)	Survivors ($n = 81$)	Nonsurvivors ($n = 48$)	P
P_{aCO_2}, mm Hg	40 (33–48)	39 (33–47)	44 (33–50)	.14
pH	7.37 (7.30–7.43)	7.39 (7.33–7.44)	7.35 (7.22–7.39)	.005
Bicarbonate, mEq/L	22.6 (20.0–25.8)	23.3 (21.5–26.0)	21.6 (18.4–24.6)	.033

Data are presented as the number (%) or the median (interquartile range). The P values are calculated using the Mann-Whitney U test for continuous variables and chi-square test or Fisher exact test for categorical variables.
SOFA = Sequential Organ Failure Assessment
ECMO = extracorporeal membrane oxygenation
PC-CMV = pressure-control continuous mandatory ventilation
VC-CMV = volume-control continuous mandatory ventilation
IBW = ideal body weight
PIP = peak inspiratory pressure
* Calculated as breathing frequency × tidal volume.
† Calculated as PIP, PEEP.
‡ Calculated as tidal volume/(PIP, PEEP).
§ Calculated as 0.098 × tidal volume × breathing frequency × (PIP 1/2 × dynamic driving pressure).
‖ Calculated as (minute ventilation × P_{aCO_2})/(IBW × 100 × 37.5).

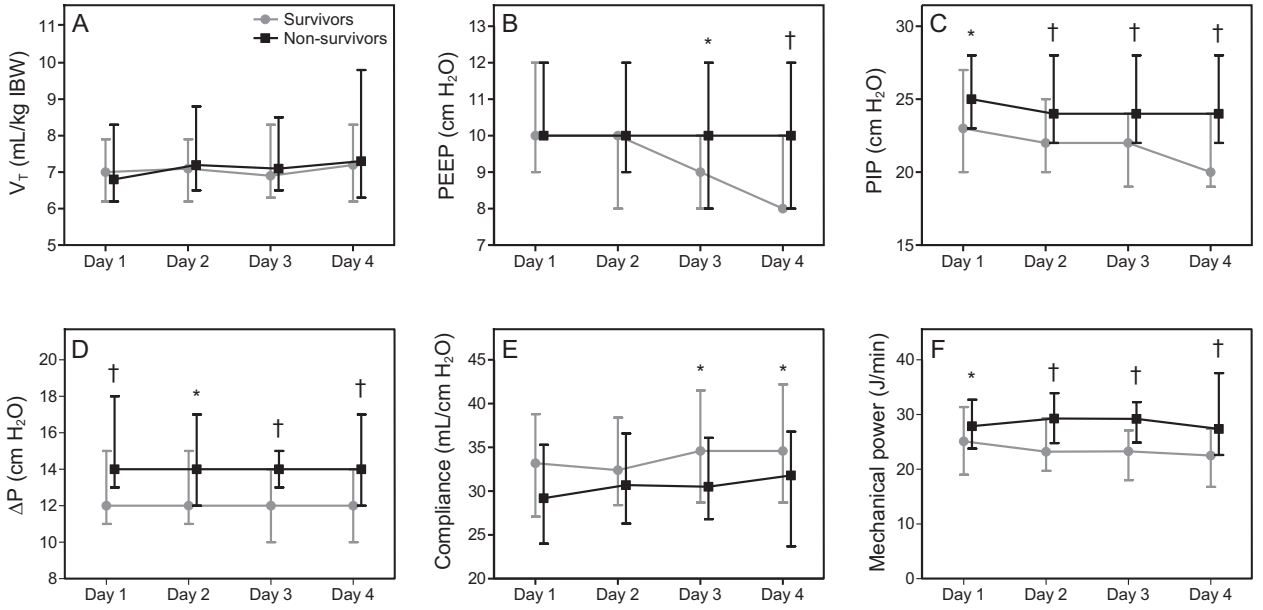

Figure 2. Serial changes in A: tidal volume (V_T), B: PEEP, C: peak inspiratory pressure (PIP), D: dynamic driving pressure (ΔP), E: dynamic compliance, and F: mechanical power in survivors and nonsurvivors during the first 4 days of mechanical ventilation. IBW = ideal body weight. *$P < .05$, †$P < .01$ when survivors and nonsurvivors were compared using Mann-Whitney U test.

mortality (Table S3, see supplementary material related to this paper at http://rc.rcjournal.com).

Characteristics, Ventilation Parameters, and Outcomes According to NMB Use

The NMB group had shorter median time from hospital admission to initiation of mechanical ventilation and lower median serum creatinine than the no NMB group (Table S4, see supplementary material related to this paper at http://rc.rcjournal.com). All subjects in whom prone positioning was performed required NMB. During the first 4 d of mechanical ventilation, both groups received a median $V_T < 8.0$ cm H_2O, but the values were significantly lower in the NMB group (Fig. 3). The median PIP, ΔP, and mechanical power values were also lower in the NMB group, but the difference did not reach statistical significance. Among the clinical outcomes, the NMB group had lower rates of ICU, hospital, and 60-d mortalities; a higher rate of ventilator weaning; and a lower rate of tracheostomy (Table 3). The survival curves for the NMB and no NMB groups

Table 2. Univariate and Multivariate Analyses of Factors Associated With ICU Mortality

	Unadjusted Odds Ratio (95% CI)	*P*	Adjusted Odds Ratio* (95% CI)	*P*
Age, y	1.09 (1.04–1.14)	< .001	1.10 (1.04–1.15)	.001
Male sex	0.80 (0.39–1.65)	.54		
Date of hospital admission				
November 30 and earlier	Reference		Reference	
December 1 and later	1.44 (0.70–2.95)	.33	0.86 (0.33–2.27)	.77
COPD	3.59 (0.63–20.40)	.15		
Time from hospital admission to mechanical ventilation	1.06 (0.97–1.15)	.18		
SOFA score at the start of mechanical ventilation	1.25 (1.09–1.43)	.002	1.17 (0.99–1.39)	.060
Corticosteroid	1.42 (0.35–5.77)	.63		
Neuromuscular blocker	0.32 (0.14–0.73)	.007	0.27 (0.09–0.81)	.02
Prone positioning	0.47 (0.16–1.39)	.17	0.56 (0.15–2.08)	.39
Creatinine†	1.25 (0.99–1.58)	.063		
Platelet count	0.99 (0.99–1.00)	.047	0.99 (0.99–1.00)	.28
Mean value from day 1–4 of mechanical ventilation				
Tidal volume	1.20 (0.97–1.49)	.10	0.99 (0.72–1.37)	.96
PEEP‡	1.20 (0.99–1.46)	.056		
PIP‡	1.21 (1.08–1.35)	.001		
Dynamic driving pressure	1.19 (1.05–1.34)	.007	1.16 (1.00–1.33)	.046
Dynamic compliance	0.97 (0.93–1.01)	.12		
Mechanical power‡	1.10 (1.04–1.16)	.001		
Ventilatory ratio	2.03 (0.93–4.41)	.08	1.69 (0.64–4.49)	.29
P_{aO_2}/F_{IO_2} at the start of mechanical ventilation	0.99 (0.99–1.00)	.16	0.99 (0.99–1.00)	.61

SOFA = Sequential Organ Failure Assessment
PIP = peak inspiratory pressure
* Adjusted for age, date of hospital admission, SOFA score at the start of mechanical ventilation, neuromuscular blocker, prone positioning, platelet count, tidal volume, dynamic driving pressure, ventilatory ratio, and P_{aO_2}/F_{IO_2} at the start of mechanical ventilation.
† Creatinine is excluded in the multivariate analysis because of high collinearity with the SOFA score at the start of mechanical ventilation.
‡ PEEP, PIP, and mechanical power are excluded in the multivariate analysis because of high collinearity.

are shown in Figure 4. The median duration of NMB use was 5 d (IQR 4–9 d) and was significantly longer in nonsurvivors (Table 1). Subjects who received NMB for ≥ 6 d (vs < 6 d) had higher rate of ICU mortality, lower rate of ventilator weaning, lower ventilator-free d at day 28, and higher rate of tracheostomy (Table S5, see supplementary material related to this paper at http://rc.rcjournal.com).

Clinical Outcomes according to Prone Positioning and V_T

Clinical outcomes did not differ when subjects were stratified according to prone positioning (yes vs no) (Table S6, see supplementary material related to this paper at http://rc.rcjournal.com) and V_T (low [≤ 6 mL/kg IBW] vs intermediate [> 6 to ≤ 8 mL/kg IBW] vs high [> 8 mL/kg IBW]) (Table S7, see supplementary material related to this paper at http://rc.rcjournal.com).

Discussion

Although previous studies have evaluated the ventilation parameters and management strategies for subjects with COVID-19 receiving mechanical ventilation,[8] there are limited data on their potential associations with mortality. This study revealed that higher ΔP, PIP, and mechanical power values during the first 4 d of mechanical ventilation were independently associated with ICU mortality. NMB use had a protective effect on mortality.

The 37% ICU mortality rate of subjects with COVID-19 requiring mechanical ventilation is in line with the 30–41% mortality rates reported in recent studies with similar subject characteristics.[20-22] Meanwhile, the median hospital length of stay of 27 d was substantially longer than the median of 14 d in the LUNG SAFE study,[23] which included subjects with non-COVID-19 ARDS. The ΔP is associated with mortality in patients with non-COVID-19 ARDS receiving mechanical ventilation.[18] In our study, ΔP was similar to non-COVID-19 ARDS and was also associated with mortality in the multivariate analysis. The changes in ΔP were determined largely by PIP changes because the PEEP changes were minimal. Interestingly, ΔP and PIP were associated with mortality despite those values being within the limits of lung-protective ventilation in our subjects,[11] even for nonsurvivors. Thus, our findings suggest that lower ΔP and PIP targets than recommended in the current guidelines might be beneficial in patients with

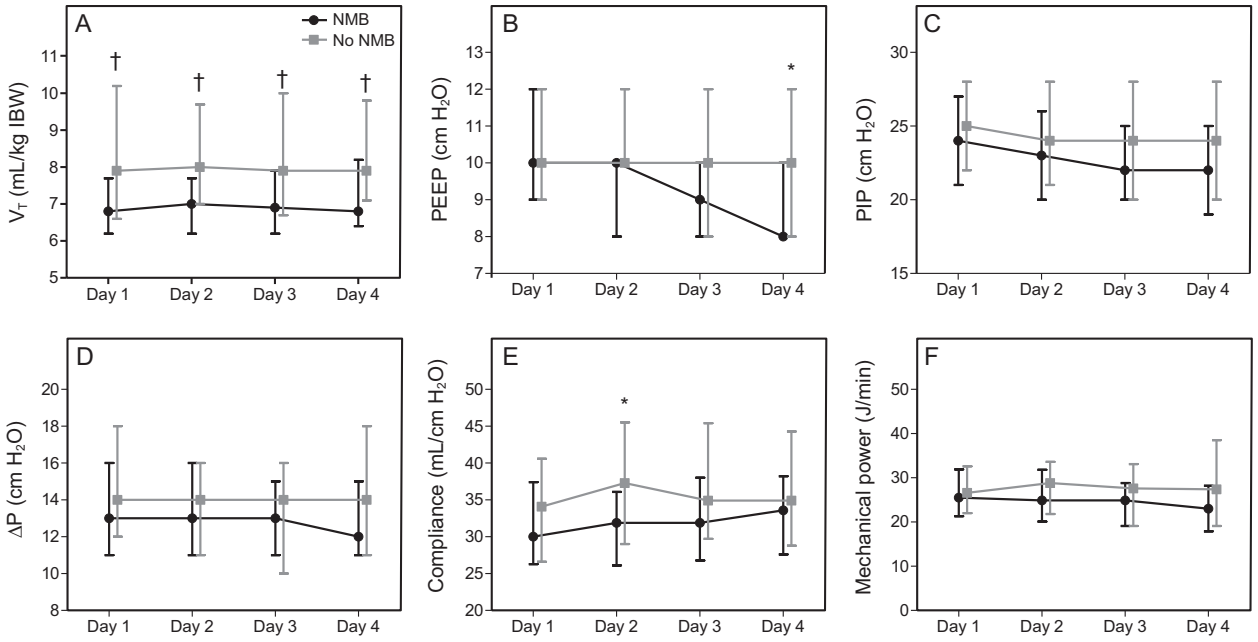

Figure 3. Serial changes in A: tidal volume (V_T), B: PEEP, C: peak inspiratory pressure (PIP), D: dynamic driving pressure (ΔP), E: dynamic compliance, and F: mechanical power in the NMB group and the no NMB group during the first 4 days of mechanical ventilation. NMB = neuromuscular blocker. IBW = ideal body weight. *$P < .05$, †$P < .01$ when the NMB and no NMB groups were compared using Mann-Whitney *U* test.

Table 3. Clinical Outcomes of Subjects According to Neuromuscular Blocker Use

	Neuromuscular Blocker ($n = 98$)	No Neuromuscular Blocker ($n = 31$)	*P*
Mortality			
ICU	30 (31)	18 (58)	.006
Hospital	35 (36)	18 (58)	.03
28-d	23 (24)	11 (36)	.19
60-d	31 (32)	16 (52)	.044
Ventilator weaning	64 (66)	13 (42)	.02
Ventilator-free days at day 28	9.0 ± 9.8	5.7 ± 8.9	.059
Hospital length of stay, d	26 (20–43)	29 (19–48)	.64
Tracheostomy	27 (28)	15 (50)	.02
Renal replacement therapy during ICU stay	21 (21)	11 (36)	.11
Superinfection	54 (55)	15 (48)	.51

Data are presented as the number (%), mean ± SD, or median (interquartile range). The *P* values are calculated using the Mann-Whitney *U* test for continuous variables and chi-square test or Fisher exact test for categorical variables.

COVID-19 ARDS. Mechanical power, which has been suggested as a risk factor for mortality in patients with ARDS,[24] was very high (median 26.0 J/min) and was associated with mortality.

Meanwhile, higher PEEP values were not associated with reduced mortality in the multivariate analysis. In ARDS, high PEEP may improve oxygenation via alveolar recruitment, although this finding can be inconsistent in COVID-19 ARDS.[25,26] The increases in PEEP levels could only improve survival through its effects on ΔP.[18] Moreover, inappropriate PEEP may result in lung overdistention, increase in dead space, and intrapulmonary shunting.[27] Some investigators have suggested that patients with COVID-19 ARDS with high compliance may be ventilated with higher V_T (7–9 mL/kg IBW) and lower PEEP (< 10 cm H_2O) than recommended.[28] The median PEEP values in survivors on day 3 and day 4 of mechanical ventilation were < 10 cm H_2O. However, the benefit of a lower PEEP in COVID-19 ARDS should be interpreted with caution because our subjects generally had low compliance.

The median compliance on day 1 of mechanical ventilation was 30.4 mL/cm H_2O, similar to findings by recent studies on subjects with COVID-19 and non-COVID-19 ARDS.[20,23,29] These observations contrast with the concept of a relatively high compliance specific to COVID-19 ARDS.[6,7] The finding that compliance values were not associated with mortality is also consistent with previous studies in COVID-19 and non-COVID-19 ARDS.[14,20,29,30] Ventilatory ratio is a surrogate marker for dead-space ventilation and is associated with an increased risk of mortality in patients with ARDS.[17] A single-center study demonstrated that ventilatory ratio was associated with hospital mortality, after adjustment for different ventilation parameters, in patients with COVID-19 ARDS.[31] However, a secondary analysis from the multi-center cohort revealed that ventilatory ratio could be a marker of disease severity but not an independent predictor of mortality.[32] Our findings

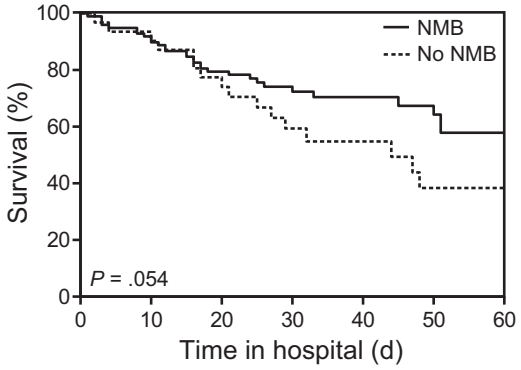

Figure 4. Kaplan-Meier survival curves during the 60 days following hospital admission according to neuromuscular blocker use. NMB = neuromuscular blocker.

also showed that ventilatory ratio increased with ARDS severity but was not associated with ICU mortality.

In mechanically ventilated patients, NMB is used to optimize endotracheal intubation, facilitate mechanical ventilation, and improve safety of prone positioning.[33] However, data regarding the efficacy and indications of NMB in patients with COVID-19 are limited. The 76% rate of NMB use in our study falls within the 72–88% rate reported in recent studies.[20,22,29,34] These rates are strikingly higher than in non-COVID-19 ARDS.[23] Unexpectedly, we found better clinical outcomes of mortality, ventilator weaning, and tracheostomy rates in the NMB group. There are several explanations for this phenomenon. First, patients with COVID-19 ARDS appear to have a high respiratory drive, which may lead to self-inflicted lung injury.[35] NMB may have been used frequently to maintain lower V_T and transpulmonary pressure. Indeed, the median V_T, PIP, ΔP, and mechanical power values in the current study were lower in the NMB group. Second, the use of NMB may be associated with a lower risk of patient-ventilator asynchrony.[36] Third, the energy requirements of patients with COVID-19 receiving mechanical ventilation are considerably high during the early period of ICU admission, and NMB may significantly decrease total energy expenditure.[37] Fourth, due to the unusual pandemic situation, there may have been inadequate staffing and training to provide lung-protective ventilation without paralytics and daily monitoring of the benefit of NMB. This may be supported by the findings that the duration of NMB use (median 5 d) was longer than recommended, and protective ventilation was only marginally achieved in the no NMB group. Nonetheless, the protective effects of NMB in ARDS have been inconsistent,[9,38] and other studies showed worse outcomes in patients with COVID-19 who received NMB.[36,39] In addition, subjects who received prolonged NMB in the current study had worse clinical outcomes, perhaps due to disease progression or the occurrence of ICU-acquired weakness. Thus, our results should be considered as hypothesis generating and need to be confirmed in larger prospective studies.

In total, 16% of the subjects was placed in prone positioning, and this rate is relatively lower than the 61–76% rate in previous studies[20,22,29] but comparable to that in the LUNG SAFE study.[23] Resource limitations, expertise, and practice differences could explain these discrepancies. Studies evaluating the efficacy of prone positioning in patients with COVID-19 are lacking, although a recent study showed that early prone positioning reduced the risk of death in patients with COVID-19 on mechanical ventilation.[40] Our study also showed lower ICU mortality and higher ventilator weaning rates in the prone group. However, these differences did not reach statistical significance. The timing of mechanical ventilation was not associated with mortality. One possible explanation is that the median time from hospital admission to initiation of mechanical ventilation was only 1 d. Further studies are required regarding the optimal timing of mechanical ventilation in COVID-19 ARDS.

The main strength of our study was the study design that assessed potential associations of various ventilation parameters and strategies with the most clinically relevant outcome of mortality. Unlike previous studies that only considered baseline ventilation parameters, serial changes in parameters during the first 4 d of mechanical ventilation may provide further information regarding the progress of COVID-19 ARDS. In addition, the daily mean values of mechanical ventilation settings were collected instead of point values to account for dynamic characteristic of mechanical ventilation.

However, the present study also had some limitations. First, residual and unmeasured confounding may have been included because of the retrospective design, and these may have biased the results. Moreover, a nonrandomized design precludes any inference of causality on associations between ΔP values and NMB use and mortality. Second, the relatively small sample size might have limited the power to detect the significant effects of prone positioning, V_T, and P_{aO_2}/F_{IO_2}. Third, data from only the first 4 d of mechanical ventilation were included in the multivariate analysis; and thus, we could not determine whether ventilation parameters after day 4 of mechanical ventilation would affect mortality. However, mechanical ventilation parameters during this period are crucial influencing factors of the prognosis of patients with ARDS.[19,41] Fourth, the mechanical ventilation settings and management were not standardized across centers; and the indications and timings of rescue therapies were unclear, which might have led to selection bias. However, the collected ventilation parameters demonstrated high similarity and adherence to current ARDS guidelines. Patient enrollment and clinical care might have differed between the centers, although KOVIDS provided a

standardized case record form and encouraged the investigators to follow the guidelines for critically ill patients with COVID-19. Fifth, some of the subjects were admitted in the early pandemic period, and overwhelmed critical care services may have biased the results. Finally, other factors such as superinfection may have influenced mortality, although the difference was not significant between survivors and nonsurvivors. Larger randomized controlled trials may address these limitations.

Conclusions

In conclusion, higher ΔP, PIP, and mechanical power values during mechanical ventilation were independently associated with ICU mortality in subjects with COVID-19 ARDS. The short-term use of NMB was associated with decreased mortality in these subjects. Further studies are needed to establish the feasibility and efficacy of lung-protective ventilation using NMB during periods of limited resources.

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