The Association Between Mechanical Power and Mortality in Ventilated Patients with Pneumonia

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Research

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Abstract

Background: Recent studies reported that mechanical power (MP) has been associated with increased mortality in patients with acute respiratory distress syndrome (ARDS). We aimed to investigate the association between 28-day mortality and MP in patients with severe pneumonia.

Methods: In total, 313 patients with severe pneumonia were enrolled. Serial MP was recorded daily for either 21 days or until ventilator support was no longer required. The associations between all variables and 28-day mortality were analyzed using binary logistic regression analyses.

Results: The ARDS group (106 patients) demonstrated lower age, higher Acute Physiology and Chronic Health Evaluation II score, lower history of diabetes mellitus, high incidences of shock and jaundice, higher MP and driving pressure on Day 1, and higher death within 28 days than the non-ARDS group. Regression analysis revealed that MP was an independent factor associated with 28-day mortality (odds ratio, 1.041; 95% confidence interval, 1.013-1.071). MP persisted high in non-survivors and low in survivors among the ARDS group, the non-ARDS group and all patients.

Conclusions: MP was associated with the 28-day mortality in ventilated patients with severe pneumonia both in the ARDS and non-ARDS groups. MP had better predicted value for 28-day mortality than driving pressure.

Background

Ventilated patients with inappropriate ventilator settings may further develop lung injury. Studies have suggested several lung protective strategies to minimize ventilator-induced lung injury (VILI) [1-3]. These studies recommend specific mechanical ventilation settings for patients with or without acute respiratory distress syndrome (ARDS), including (1) low tidal volume ventilation (6 mL/kg predicted body weight [PBW]), (2) relatively higher positive end-expiratory pressure (PEEP), and (3) using an upper limit goal for end-inspiratory plateau pressures of 30 cm H_2O [1,3,4] .

Amato's study reported that driving pressure was most strongly associated with survival in patients with ARDS who received mechanical ventilation with different combinations of tidal volume and PEEP [5]. In patients with severe ARDS receiving extracorporeal membrane oxygenation (ECMO), higher driving pressure during the first 3 days of ECMO support was independently associated with increased mortality [6]. In a rat-model of open abdominal surgery, lower driving pressure was associated with reduced lung damage [7]. In patients with severe pneumonia without ARDS, higher driving pressure was associated with 28-day mortality [8]. Thus, driving pressure could be used as a non-invasive method to predict lung injury in patients with and without ARDS.

Recently, a new concept of safe mechanical ventilation using mechanical power (MP) was introduced [9]. The MP enrolled several underlying relevance. First, it imports static compliance inducing VILI [10]. Second, it accounts for the final effect of PEEP. The PEEP is positively associated with VILI, but PEEP may

decrease the lung-dependent VILI by reducing lung inhomogeneity and intratidal alveolar collapse–decollapse. Third, transpulmonary MP increased with the respiratory rate (RR) [11]. Serpa et al. reported that MP of ventilation in the first 48 h is associated with mortality in critically ill patients in two observational cohorts. In patients with ARDS, initial MP was also associated with mortality [12-14]. These four studies all used simplified equation proposed by Gattinoni et al. to calculate MP in patients with volume-controlled ventilation [9,15].

Therefore, we used a consecutively sampled observational cohort data of patients with severe pneumonia to identify three questions: (1) the association between MP and 28-day mortality in patients with pressure-controlled ventilation (PCV), (2) the predicted value of 28-day mortality between driving pressure and MP, and (3) the usefulness of the simplified equation of MP for PCV.

Methods

Subjects

The cohort study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and the need for a written informed consent was waived (96-0132B, 97-0121C, 98-1682C, 201700804B0). Patients admitted to the medical intensive care unit (ICU) at Chang Gung Memorial Hospital, Keelung from July 2007 to June 2010 due to severe pneumonia were selected. We screened 493 patients who were admitted to the ICU (Supplementary Fig. 1). In total, 313 patients were enrolled in this study, and 180 patients were excluded. The exclusion criteria included infections other than pneumonia, absence of invasive ventilator support, an unknown arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio or death on the day of admission. None of the included patients withdrew from this study. A total of 61 ARDS patients and 56 non-ARDS patients died within 28 days of ICU admission during the course of this study.

Disease definitions

The following diseases were defined at the time of admission to the ICU. Pneumonia was defined as a new abnormal infiltration on chest radiograph with respiratory symptoms or fever. Severe pneumonia was defined as pneumonia complicated by acute respiratory failure requiring intubation and mechanical ventilation with or without septic shock [16]. Sepsis and septic shock were defined according to Sepsis-3 guidelines [17]. Sepsis was defined as a suspected or documented infection with acute increase (≥2) in the Sequential Organ Failure Assessment points. Septic shock was defined as sepsis with blood lactate level >18 mg/dL and hypotension that was unresponsive to fluid resuscitation, requiring vasopressors to maintain mean arterial pressure ≥65 mm Hg during the first 3 days following ICU admission. Acute renal failure was diagnosed by a rapidly increasing serum creatinine level ³ 0.5 mg/dL over the baseline value [18]. Disease severity was assessed with the Acute Physiology and Chronic Health Evaluation (APACHE) II score [19]. ARDS was defined according to the Berlin definition [20]. ARDS was evaluated via chest

radiographs obtained after intubation with ventilator support. Patients who were initially diagnosed as non-ARDS and developed ARDS within 1 week were classified as ARDS. Patients who were initially diagnosed as non-ARDS and developed ARDS after 1 week were still classified as non-ARDS. Patients who survived for at least 28 days since ICU admission were considered as survivors.

Treatment

Standard therapies, including fluid resuscitation, broad-spectrum antibiotic administration, infected fluid drainage, blood transfusion, sedation/paralysis, blood glucose control, hemodialysis, stress ulcer prophylaxis, and basic support were provided to all patients according to the recommended guidelines [21,22]. The initial broad-spectrum antibiotics were selected based on either the Taiwan Guidelines for Pneumonia Management (2007 version) or the Guidelines of the American Thoracic Society [16,23].

Ventilator settings

In our hospital, volume-controlled ventilation (VCV) was not used to prevent VILI due to rapid change of peak pressure. Following intubation, all patients were routinely administered by PCV with a separate target tidal volume of approximately 6 and 10 mL/kg PBW for patients with ARDS and non-ARDS, respectively. The goal was to maintain an inspiratory plateau pressure (Pplat) of less than 30 cm H_2O. The PEEP level and FiO_2 were adjusted to maintain PaO_2 greater than 60 mmHg or oxygen saturation by pulse oximetry (SpO_2) greater than 90%. Ventilator settings were adjusted after 2 h of the first setting. Ventilator weaning and adjustment were performed at regular intervals (every 8 h) and as necessary, based on the general weaning guidelines and clinical practice of our respiratory therapy department [24].

Data records

ICU admission date was considered as Day 0. The next date of ICU admission was defined as Day 1. The following patient data were recorded within 24 h after admission: age, sex, medical history, and APACHE II score. Adverse events were recorded within the first 3 days following admission. Arterial blood gases demonstrating the lowest PaO_2/FiO_2 ratio were used within 24 h after intubation with ventilator support. Driving pressure (ΔP) was defined as the difference between Pplat and PEEP [25]. MP for PCV was calculated according to the simplified equation [15,26], using RR, tidal volume size (L) (V_T), ΔP_{insp} and PEEP: $\mathrm{MP_{PCV}}\ (\mathrm{J/min}) = 0.098 \times \mathrm{RR} \times V_T \times \left(\Delta P_{insp} + \mathrm{PEEP}\right)$, where ΔP_{insp} is the change in airway pressure during inspiration. Driving pressures and MP were recorded every 8 h per day. Serial mean data of ΔP_{insp}, RR, V_T and PEEP were recorded daily for either 21 days or until the ventilator support was no longer required.

Statistical analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows (SPSS, Inc., Illinois, USA). Differences in the continuous variables between the two groups were analyzed using Student's t-test. Differences in categorical variables between the ARDS and non-ARDS groups were compared using the Pearson chi-squared test or Fisher's exact test. Univariate binary logistic regression model analyses were performed to study the association between the 28-day mortality and all variables. Statistically significant variables were entered into a multivariate binary logistic regression model to assess their independent contribution to the outcome. The cut-off value of driving pressure and MP on Day 1 to predict 28-day mortality was identified according to the receiver operating characteristic (ROC) curve (Fig. 1) with areas of 0.628 ($p<0.001$) and 0.730 ($p<0.001$) under the ROC curve, respectively. The area under the ROC curve of MP normalized to PBW (MP/PBW) was also calculated, which was 0.734 ($p<0.001$). If the cutoff value for driving pressure was set at 19 cm H_2O, the sensitivity and specificity were 58.1% and 57.7%, respectively. If the cutoff value for MP was set at 27 J/min, the sensitivity and specificity were 65.0% and 64.3%, respectively. A Kaplan-Meier graph was plotted to analyze the probability of death after ICU admission. Survival times of MP between MP < 27 J/min and MP ≥ 27 J/min were compared using log-rank test. P values less than 0.05 were considered statistically significant.

Results

Table 1 demonstrates the baseline clinical characteristics of patients with pneumonia between ARDS and non-ARDS. Some patients with the PaO_2/FiO_2 ratio less than 300 mm Hg were classified as non-ARDS due to the absence of bilateral opacities on chest radiography. The ARDS group had lower age and higher APACHE II score, MP, and driving pressure than the non-ARDS group. The incidences of shock, jaundice and death were higher and mean age was lower in the ARDS group than those in the non-ARDS group. In total, pathogens were identified in 88.2% of patients (Supplementary Table 1). The most frequently isolated pathogens, in decreasing order, were *Pseudomonas aeruginosa*, *Staphylococcus aureus,* *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Escherichia coli*.

Table 1

Clinical characteristics and outcomes of ventilated patients with pneumonia, according to subgroups

Characteristics	ARDS (N=106)	Non-ARDS (N=207)	All patients (N=313)
Age, years*	69.1 ± 16.3	75.1 ± 13.1†	73.1 ± 14.5
APACHE II score*	27.6 ± 8.7	25.3 ± 6.8†	26.1 ± 7.6
Sex, No. (%)			
Male	75 (70.8)	137 (66.2)	101 (67.7)
Female	31 (29.2)	70 (33.8)	212 (32.3)
History, No. (%)			
COPD	24 (22.6)	49 (23.7)	73 (23.3)
CHF	7 (6.6)	20 (9.7)	27 (8.6)
Hypertension	40 (37.7)	97 (46.9)	137 (43.8)
Liver cirrhosis	10 (9.4)	13 (6.3)	23 (7.3)
Hemodialysis	6 (5.7)	21 (10.1)	27 (8.6)
Diabetes mellitus	19 (17.9)	68 (32.9)†	87 (27.8)
PaO_2/FiO_2 ratio (mm Hg)*	133.9 ± 70.3	350.6 ± 199.1†	277.2 ± 195.9
Adverse events, No. (%)			
Shock	59 (55.7)	68 (32.9)b	127 (40.6)
Acute renal failure	47 (44.3)	78 (37.7)	125 (39.9)
GI bleeding	18 (17.0)	27 (13.0)	45 (14.4)
Thrombocytopenia	45 (42.5)	65 (31.4)	110 (35.1)
Jaundice	15 (14.2)	9 (4.3)†	24 (7.7)
Mechanical power (J/min) on Day 1*	31.7 ± 10.7	25.8 ± 12.2†	27.8 ± 12.0
Driving pressure (cm H_2O) on Day 1*	19.6 ± 4.5	18.1 ± 4.5†	18.6 ± 4.6
Death within 28 days, No. (%)	61 (57.5)	56 (27.1)†	117 (37.4)

Abbreviations: ARDS = acute respiratory distress syndrome; APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; PaO_2 = arterial partial pressure of oxygen; FiO_2 = fraction of inspired oxygen; GI = gastrointestinal

*Data are shown as mean ± standard deviation.

†p<0.05 compared with the ARDS group using the Mann-Whitney U test or chi-squared test

According to the binary logistic regression model, the variables that were independently associated with the 28-day mortality were ARDS (odds ratio [OR], 2.671; 95% confidence interval [CI], 1.502 – 4.749), thrombocytopenia (OR, 2.410; 95% CI, 1.343 – 4.328) and MP (OR, 1.041; 95% CI, 1.013 – 1.071) (Table 2). ARDS, thrombocytopenia, and MP were positively correlated.

Table 2

Binary logistic regression to analyze the independent factors for 28-day mortality

Variables	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Age	0.985 (0.970-1.001)	0.058		
APACHE II score	1.091 (1.055-1.128)	<0.001	1.039 (0.998-1.083)	0.064
Male	0.985 (0.604-1.607)	0.951		
COPD	0.906 (0.525-1.563)	0.722		
Congestive heart failure	0.824 (0.358-1.900)	0.650		
Hypertension	0.530 (0.330-0.851)	0.009	0.628 (0.356-1.108)	0.108
Liver cirrhosis	2.824 (1.181-6.749)	0.020	1.467 (0.471-4.565)	0.508
Hemodialysis	1.913 (0.866-4.227)	0.109		
Diabetes mellitus	0.587 (0.344-1.003)	0.051		
ARDS	3.655 (2.234-5.980)	<0.001	2.671 (1.502-4.749)	0.001
Shock	3.859 (2.380-6.257)	<0.001	1.594 (0.878-2.893)	0.125
Acute renal failure	2.522 (1.573-4.042)	<0.001	1.546 (0.865-2.763)	0.141
Gastrointestinal bleeding	2.151 (1.137-4.068)	0.019	1.575 (0.678-3.656)	0.291
Thrombocytopenia	4.194 (2.560-6.872)	<0.001	2.410 (1.343-4.328)	0.003
Jaundice	3.056 (1.292-7.227)	0.011	0.872 (0.291-2.614)	0.807
Mechanical power (J/min) on Day 1	1.076 (1.051-1.101)	<0.001	1.041 (1.013-1.071)	0.004
Driving pressure (cm H_2O) on Day 1	1.126 (1.065-1.190)	<0.001	1.051 (0.978-1.130)	0.174
Abbreviations: OR = odds ratio; CI = confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; ARDS = acute respiratory distress syndrome				

The MP persisted high in non-survivors and low in survivors among the ARDS group, the non-ARDS group, and all patients (Fig. 2). In all patients, MP in non-survivors was higher than in survivors during the 21 days recorded except Day 18. In the ARDS group, MP in non-survivors was higher than in survivors on Days 1-11, 16, and 20. In the non-ARDS group, MP in non-survivors was higher than in survivors on Days 1-14, and 17. The Kaplan-Meier curves showed the possibility of survival until 28 days after ICU admission for MP on Day 1 above and below 27 J/min among the ARDS group, the non-ARDS group, and

all patients (Fig. 3). Patients with MP < 27 J/min on Day 1 demonstrated significantly higher survival rates than those with MP ≥ 27 J/min in all patients and the non-ARDS group ($p<0.001$). In the ARDS group, patients with MP < 27 J/min did not show higher survival rate than those with MP ≥ 27 J/min ($p=0.067$).

Discussion

According to multivariate regression analysis, MP on Day 1 and ARDS were independent factors associated with 28-day mortality. Patients with lower MP on Day 1 had better chances to survive compared to those with higher MP on Day 1. In initial univariate regression analysis, driving pressure on Day 1 was a factor associated with 28-day mortality. However, the significant association was not observed in multivariate regression analysis. In ROC curves of the ARDS group, driving pressure did not discriminate survivors from non-survivors, but driving pressure could discriminate between survivors and non-survivors in all patients and the non-ARDS group. It suggests that ARDS confounds the association between driving pressure and 28-day mortality.

Our study first found that ventilated patients with pneumonia with or without ARDS demonstrated higher serial MP in non-survivors than in survivors from Day 1 to Day 11 of ICU admission. The MP between survivors and non-survivors was similar only on Day 18 of ICU admission in all patients statistically. Our study not only confirmed that baseline MP was associated with mortality [11-14], but also found that the association persisted for 11 days. In the Kaplan-Meier curves of the ARDS group, the two curves were similar within the first 10 days and separated later evidently. This implied that the benefit of lower MP required a period of time to develop in patients with more severe pneumonia. Furthermore, deep sedation significantly reduced MP in patients with moderate to severe ARDS, thereby reducing the occurrence of VILI [14]. All the above suggested that MP might be the cause of VILI, resulting in increased mortality rate. Certainly, it is reasonable since all mechanical factors in ventilation-tidal volume, driving pressure, flow, resistances, RR, and PEEP-are different components of a unique physical variable, which is the energy delivered into the lung. Up to now, there is no study reporting the results of mortality using MP as a guide of ventilator settings to manage critically ill patients. Further studies are required to elucidate whether MP is a predictor or cause.

In our study, driving pressure was not an independent factor associated with 28-day mortality in ventilated patients with severe pneumonia, but MP was an independent factor. In experimental mild ARDS of rats, even at low V_T, high MP promoted VILI [27]. In a computational study, MP showed a strong correlation with the relative risk of death across all ranges of driving pressures and PEEP [28]. Moreover, the areas under the ROC of MP were higher than those of driving pressure among the ARDS group, the non-ARDS group, and all patients in our study. This implied that MP might be a better predictor of 28-day mortality than V_T or driving pressure in patients with severe pneumonia with or without ARDS. The positive and negative predictive values of MP using the cutoff value ≥ 27 J/min for 28-day mortality were 50.1% and 75.4%, respectively. This suggests that approximately 75% of ventilated patients with severe pneumonia and low MP would survive for 28 days. Discrimination ability of MP and MP normalized to

PBW in predicting 28-day mortality was nearly similar in this study. This result was similar to that of Zhang's study, which found 0.747 and 0.751 of areas under ROC curve for MP and MP normalized to PBW, respectively [12]. For easy use in routine clinical practice, calculation of MP instead of MP normalized to PBW might be sufficient.

The MP was first determined with the simplified formula suggested by Gattinoni et al. for VCV: $\mathrm{MP_{VCV}}\ (\mathrm{J/min}) = 0.098 \times \mathrm{RR} \times V_T \times \left(\mathrm{peak\ \ pressure} - \frac{1}{2}\mathrm{driving\ \ pressure}\right)$ [9]. As the equation for calculation of MP is based on the assumption of VCV with a linear increase of airway pressure during inspiration, it is not suitable for calculating MP during PCV [29]. For PCV, two accurate equations have been proposed, but both require using some parameters (resistances, respiratory system compliance) that are not usually continuously quantified and displayed in the ventilator [26,30]. Finally, we used the simplified formula for PCV proposed by Becher et al. [26] since this equation had acceptable accuracy and routine record by our respiratory therapeutist. Our study demonstrated that this simplified formula was easy to use, and the MP calculated had acceptable discrimination for 28-day mortality in ventilated patients with severe pneumonia.

The most important current recommendation to provide lung protective ventilation in ventilated patients with pneumonia is low tidal volumes [3]. However, despite the use of lung protective ventilation proposed by ARDSnet protocol, overall ICU and hospital mortality of ARDS patients is still higher than 40% [31]. Low tidal volume ventilation did not show estimated benefit in patients with ARDS. It seems that only low tidal volume ventilation is insufficient to protect the lung. Since 2015, Amato et al. reported the results of a retrospective analysis and concluded that driving pressure was better associated with 60-day mortality in patients with ARDS than tidal volume [5]. Following this, Guerin et al. demonstrated this viewpoint [32], and a meta-analysis from Neto et al. showed that an increase of driving pressure was associated with more postoperative pulmonary complications [33]. Our previous study further found that higher driving pressure was associated with 28-day mortality in patients with severe pneumonia without ARDS [8]. In this study, results showed that MP on Day 1 was independently positively associated with 28-day mortality and had better predicted value than driving pressure either in patients with ARDS or without ARDS. Our results support the hypothesis that a marker with several important indices is better than that with one index. The predicted value of MP, which included tidal volume, inspiratory pressure, RR, and PEEP, was better than driving pressure alone.

This study has an important strength. We presented serial data over the course of 21 days with consistent results during the first 11 days in patients with or without ARDS. This study also has three limitations. First, this study was a single-center trial without thousands of case number. More studies are required to confirm our results. Second, there were significantly few patients who developed ARDS after a period of 1 week. Third, chest radiograph findings might have been misinterpreted considering the presence of unilateral infiltrates or opacities due to the limitations of traditional chest radiography. Computed tomography may be a preferred technique to detect lung injury. Considering the similar results between the ARDS and non-ARDS groups, it did not significantly influence the final conclusion.

Conclusions

Our findings imply that MP may be an important factor associated with the 28-day mortality in ventilated patients with severe pneumonia both in the ARDS and non-ARDS groups. The MP, which included tidal volume, inspiratory pressure, RR, and PEEP, had better predicted value for 28-day mortality than driving pressure. The simplified formula for PCV to calculate MP was useful in patients ventilated with PCV mode.

Abbreviations

VILI: ventilator-induced lung injury; ARDS: acute respiratory distress syndrome; PBW: predicted body weight; PEEP: positive end-expiratory pressure; ECMO: extracorporeal membrane oxygenation; MP: mechanical power; RR: respiratory rate; PCV: pressure-controlled ventilation; ICU: intensive care unit; PaO_2: arterial partial pressure of oxygen; FiO_2: fraction of inspired oxygen; APACHE: Acute Physiology and Chronic Health Evaluation; VCV: volume-controlled ventilation; Pplat: plateau pressure; SpO_2: oxygen saturation by pulse oximetry; ΔP: Driving pressure; V_T: tidal volume; ΔP_{insp}: the change in airway pressure during inspiration; SPSS: Statistical Package for the Social Sciences; ROC: receiver operating characteristic; OR: odds ratio; CI: confidence interval

Declarations

Ethics approval and consent to participate

This cohort study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and the need for a written informed consent was waived (96-0132B, 97-0121C, 98-1682C, 201700804B0).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they do not have any financial or personal relationships that might inappropriately influence their actions and create a conflict of interest relative to the content of this manuscript.

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Authors' contributions

HW and KK designed and conducted this study. HW, CC, LC, SL, SL, KC and KK helped in the data analysis and interpretation of the results. PL helped in statistical analysis. HW prepared the manuscript.

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Figures

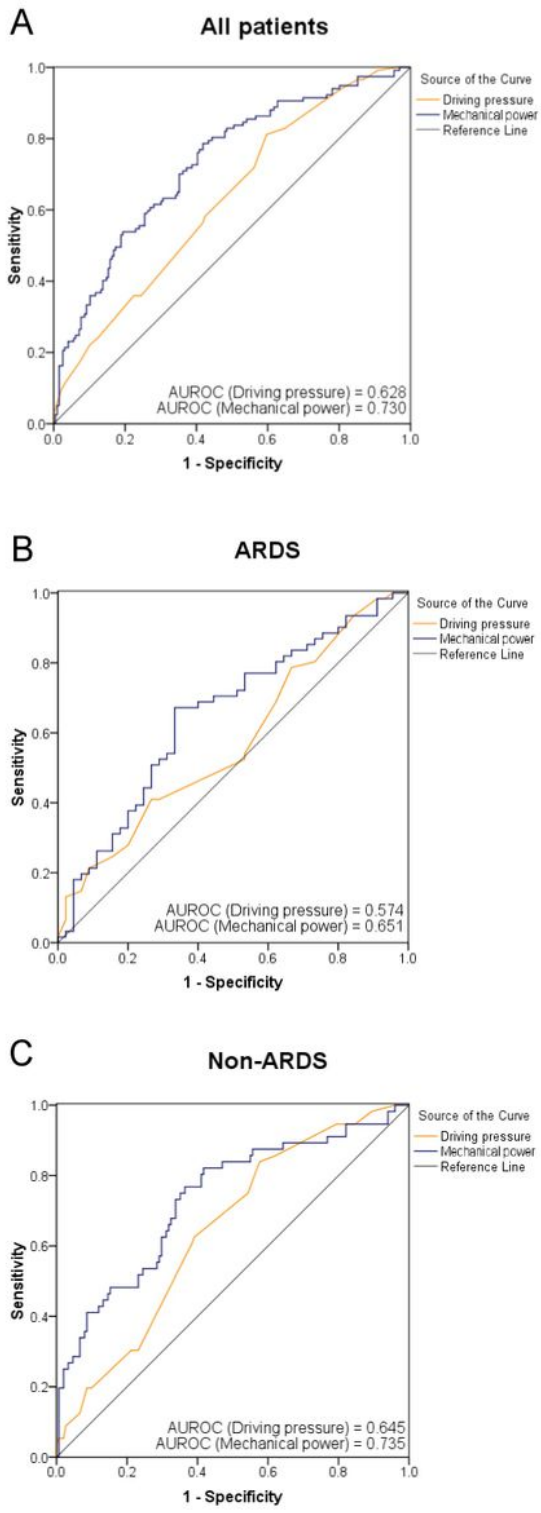

Figure 1

Receiver operating characteristic (ROC) curves of driving pressure and mechanical power on Day 1 for 28-day mortality among all patients (A), the acute respiratory distress syndrome (ARDS) group (B), and the non-ARDS group (C). The areas under the ROC (AUROC) were calculated. The AUROC for driving pressure and mechanical power were 0.628 (95% confidence interval [CI], 0.566-0.691; p<0.001) and 0.730 (95% CI, 0.673-0.787; p<0.001), respectively, in all patients. The AUROC for driving pressure and mechanical power

were 0.574 (95% CI, 0.464-0.684; p=0.197) and 0.651 (95% CI, 0.545-0.757; p=0.008), respectively, in ARDS patients. The AUROC for driving pressure and mechanical power were 0.645 (95% CI, 0.565-0.725; p=0.001) and 0.735 (95% CI, 0.655-0.814; p<0.001), respectively, in non-ARDS patients.

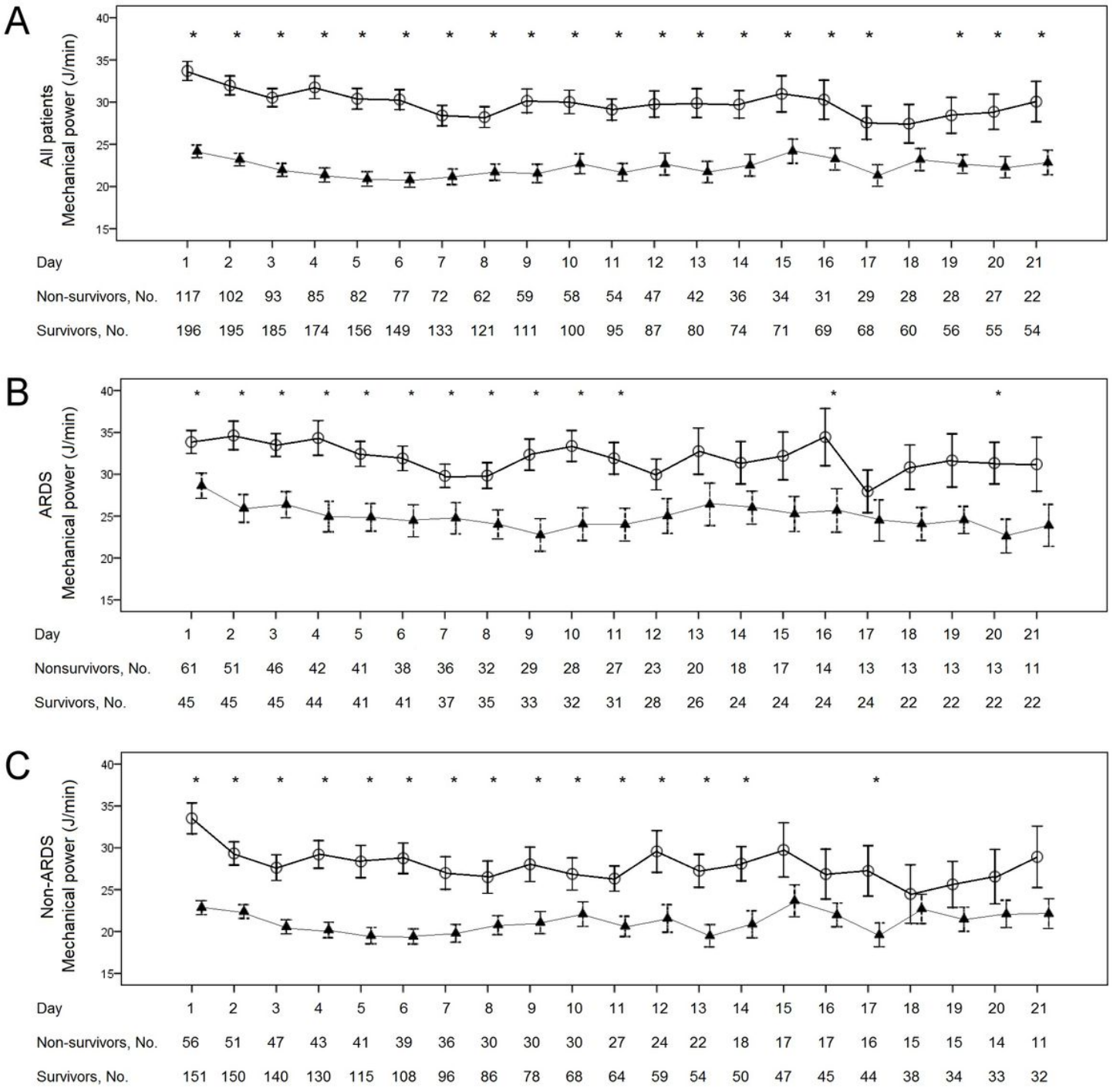

Figure 2

Error bars of serial mechanical powers (J/min, mean ± 1 standard error mean) from Day 1 to Day 21 between non-survivors and survivors. Asterisks represent significant differences between non-survivors and survivors using Mann-Whitney U test. Hollow circle bars represent non-survivors, and solid triangle bars represent survivors. Serial mechanical powers were higher in non-survivors than in survivors during

most of the 21-day period among all patients (A), the acute respiratory distress syndrome (ARDS) group (B), and the non-ARDS group (C).

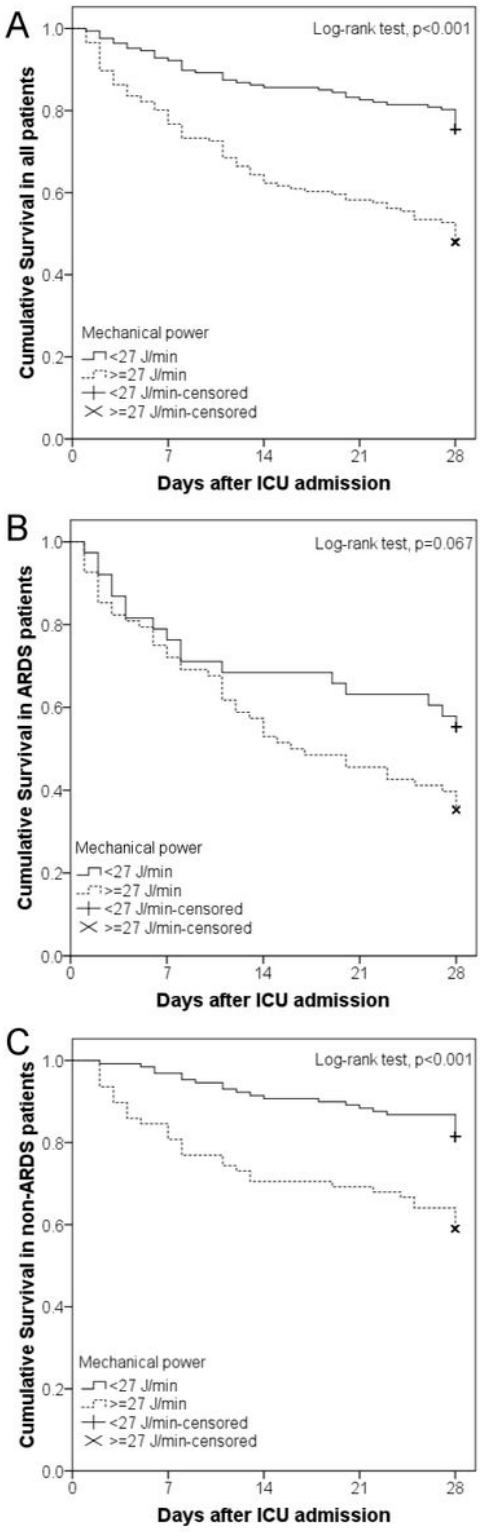

Figure 3

Kaplan-Meier graphs of 28-day intensive care unit (ICU) cumulative survival among all patients (A), the acute respiratory distress syndrome (ARDS) group (B), and the non-ARDS group (C) according to mechanic power on the Day 1 of ICU admission (≥ 27, < 27 J/min).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.docx
- SuppFig1Flowchart.tif