Factors associated with prolonged weaning from mechanical ventilation in medical patients

Soo Jin Na, Ryoung-Eun Ko, Jimyoung Nam, Myeong Gyun Ko and Kyeongman Jeon

Abstract

Background: Patients who need prolonged mechanical ventilation (MV) have high resource utilization and relatively poor outcomes. The pathophysiologic mechanisms leading to weaning failure in this group may be complex and multifactorial. The aim of this study was to investigate the factors associated with prolonged weaning based on the Weaning Outcome according to a New Definition (WIND) classification.

Methods: This is a prospective observational study with consecutive adult patients receiving MV for at least two calendar days in medical intensive care units from 1 November 2017 to 30 September 2020. Eligible patients were divided in a non-prolonged weaning group, including short and difficult weaning, and in a prolonged weaning group according to the WIND classification. The risk factors at the time of first separation attempt associated with prolonged weaning were analyzed using a multivariable logistic regression model.

Results: Of the total 915 eligible patients, 172 (18.8%) patients were classified as prolonged weaning. A higher proportion of the prolonged weaning group had previous histories of endotracheal intubation, chronic lung disease, and hematologic malignancies. When compared with the non-prolonged weaning group, the median duration of MV before the first spontaneous breathing trial (SBT) was longer and the proportion of tracheostomized patients was higher in prolonged weaning group. In addition, the prolonged weaning group used higher peak inspiratory pressures and yielded lower PaO2/FiO2 ratios at the day of the first SBT compared with the non-prolonged weaning group. In multivariate analyses, the duration of MV before first SBT (adjusted odds ratio [OR] = 1.14, 95% confidence interval [CI] = 1.06–1.22, p < 0.001), tracheostomy state (adjusted OR = 1.95, 95% CI = 1.04–3.63, p = 0.036), PaO2/ FiO2 ratio (adjusted OR = 1.00, 95% CI = 0.99–1.00, p = 0.023), and need for renal replacement therapy (adjusted OR = 2.68, 95% CI = 1.16–6.19, p = 0.021) were independently associated with prolonged weaning. After the exclusion of patients who underwent tracheostomy before the SBTs, similar results were obtained.

Conclusion: Longer duration of MV before the first SBT, tracheostomy status, poor oxygenation, and need for renal replacement therapy at the time of first SBT can predict prolonged weaning.

Trial registration: ClinicalTrials.gov Identifier NCT05134467.

Keywords: classification, intensive care unit, mechanical ventilation, risk factors, treatment outcome, ventilator weaning

Received: 5 February 2022; revised manuscript accepted: 15 July 2022.
Background

Mechanical ventilation (MV) is a commonly used intervention for respiratory support in intensive care units (ICUs). Although advances in critical care have led to improved survival from acute illness, the number of patients requiring prolonged MV after acute respiratory failure is increasing, thereby leading to increased healthcare costs, morbidity, and mortality. Therefore, it is necessary to make predictions for the patients who will require prolonged MV to inform them, formulate surrogate decision-making, and identify targets for future interventions. Previous studies have sought to identify these predictors; however, their results are difficult to generalize because they examined varying durations of MV and specific patient populations.

The definition of prolonged MV has been varied depending on the study, but most studies have been based on the total duration of MV ranging from 1 day to 4 weeks. MV is used in patients with various medical conditions that are not accompanied by impaired pulmonary function such as cardiac arrest, altered mental status, or postoperatively, however. In addition, there may be differences in the timing or technique of the MV separation attempt depending on the hospital’s policy or physician’s practice pattern. Therefore, it may be reasonable to focus on the difficulty or duration of weaning process rather than the entire duration of MV in terms of evaluating MV-related outcomes. The European Respiratory Society Task Force has defined prolonged weaning as the need for the weaning process for >7 days after the first spontaneous breathing trial (SBT), but it has limitations in classifying patients with various settings encountered in real practice, such as tracheostomized patients. Recently, researchers in the Weaning Outcome according to a New Definition (WIND) study suggested a new classification scheme that can overcome these limitations in predicting the prognosis of patients who receive MV. Therefore, the objective of this prospective cohort study was to evaluate the characteristics of patients who require prolonged MV and to identify predictive factors related to prolonged weaning by the WIND classification in patients admitted to the medical ICU.

Methods

Study population

All consecutive patients admitted to two medical ICUs and those requiring MV for more than 24 h from November 2017 were prospectively registered at Samsung Medical Center (a 1989-bed tertiary referral hospital) in Seoul, South Korea. For this study, we excluded from the analysis those patients who were treated with extracorporeal membrane oxygenation for respiratory support (n = 37), did not undergo SBT before extubation (n = 317), or were withdrawn from MV as palliative care (n = 17). Eligible patients were divided in a non-prolonged weaning group, including short and difficult weaning, and in a prolonged weaning group according to the WIND classification scheme (Figure 1).

The institutional review board of the Samsung Medical Center approved this study (IRB no. 2017-08-141-009) and waived the requirement for informed consent because of the observational nature of the research. In addition, patient information was anonymized and de-identified prior to analysis.

Standardized weaning process

Since 2010, the two medical ICUs in our hospital have been using the same standardized weaning programs based on a respiratory care practitioners-driven, protocol-directed approach; the details of the weaning process have been described in our previous studies. Every morning, respiratory care practitioners assessed a patient’s readiness to be weaned from MV in all patients who received MV for more than 24 h. First, we comprehensively evaluated the patient’s condition, including improvement of the underlying cause of respiratory failure, clinical stability, and adequacy of pulmonary function and oxygenation. If the patient fulfilled all of the criteria of readiness for weaning trials (Supplementary Table S1), SBT was conducted according to the protocol to assess the ability of the patient for spontaneous breathing; if the patient did not fulfill the criteria, no further weaning process was performed on that day. Our hospital performed the T-piece trial, in which supplemental oxygen was provided through a T-piece connected to an endotracheal tube or tracheostomy tube, on all patients until July 2019. From July 2019, SBT
was performed with inspiratory pressure augmentation (the ventilator was set with a pressure support of 8 cmH₂O and zero-positive end-expiratory pressure) for patients who received MV through an endotracheal tube according to the revised weaning protocol.¹⁹ The T-piece trial was conducted for patients with tracheostomy as before. Tolerance for SBT was evaluated for 30 min on the first attempt and for 2 h after the second attempt, regardless of the method used. If a sign of SBT failure was identified even before the target duration, however, the trial was immediately stopped. When the patient satisfied all the criteria for successful SBT (Supplementary Table S2), extubation was performed directly, and supplemental oxygen was provided by a high-flow nasal cannula for at least 24 h in patients with an endotracheal tube; administration of supplemental oxygen was continued through a T-piece system in patients with tracheostomy. Decisions about when and how to perform a tracheostomy were left to the discretion of the clinicians and were not guided by a prescribed algorithm.

Weaning outcomes
Successful weaning was defined as (1) extubation without death or reintubation within the next 7 days irrespective of whether non-invasive ventilation was used postextubation, or whether the patients were discharged from the ICU without invasive MV within 7 days, whichever came first for intubated patients and (2) spontaneous ventilation through tracheostomy without any MV during 7 consecutive days, or discharged with spontaneous breathing, whichever came first in the cases of tracheostomized patients.¹⁵ The date of the successful weaning was counted retrospectively to the actual day of extubation after the patient had completed 7 days without reintubation or was discharged earlier without reintubation.

The weaning outcomes were classified in three categories using the WIND classification¹⁵: (1) short weaning when the first separation attempt resulted in the termination of the weaning process within a day, (2) difficult weaning when the weaning process was completed after more than 1 day but in less than 1 week after the first separation attempt, and (3) prolonged weaning when the weaning was still not terminated 7 days after the first separation attempt (by successful separation or death), respectively. The weaning process was considered to be terminated if the patient was successfully separated from MV or if the patient died.

Figure 1. Scheme of group distribution.
ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; SBT, spontaneous breathing trial.
Data collection
A trained study coordinator reviewed hospital medical records and obtained clinical, laboratory, and outcome data. Patient demographics and the major reason for MV were assessed by the physician responsible for care and were recorded on the day of the initiation of MV. Details of the patient’s readiness for weaning trials and the methods and results of SBT were recorded in the format specified by the respiratory care practitioners. Patient vital signs – including blood pressure, heart rates, respiratory rates, and transcutaneous oxygen saturation – were continuously monitored and automatically recorded every hour. There was no protocol for the time at which blood gas analysis was performed except at the end of SBT, but arterial blood was usually obtained for blood gas analyses at approximately 5am every day. The values of the MV setting and respiratory parameters were synchronized to the hospital electronic medical chart and recorded every hour, and we collected the values at 8am. Patients were followed up until discharge from hospital and clinical outcomes, including weaning success, respiratory status at ICU discharge, ICU length of stay, and hospital mortality, were identified based on a review of the medical records.

Statistical analysis
Data are presented as medians and interquartile ranges (IQRs) for continuous variables and as numbers and percentages for categorical variables. Comparisons of clinical characteristics and weaning outcomes between the prolonged weaning group and non-prolonged weaning group was carried out using the Mann–Whitney U test for continuous variables, and the χ² or Fisher’s exact test for categorical variables, wherever applicable. To identify risk factors for prolonged weaning, we performed logistic regression analyses. Variables that appeared to be related in the univariate logistic regression analyses with a p-value of <0.1 were considered in multivariate regression models. Because tracheostomy may have been performed in patients with expected prolonged weaning, we performed additional multivariate analysis after the exclusion of tracheostomized patients according to the physician’s judgment. The results of logistic regression models were reported as odds ratios (ORs) of each variable with their 95% confidence intervals (CIs). For all analyses, a two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed using the software STATA (version 16.0, Stata Corporation, College Station, TX, USA).

Results
During the study period, a total of 1286 patients were eligible, but 371 (28.8%) patients were excluded by the exclusion criteria. The final cohort included 915 patients with a median age of 67 (IQR = 57–75) years, and 594 patients (64.9%) were male. According to the WIND classification, 561 (61.3%) patients were classified as short weaning, 182 (19.9%) as difficult weaning, and 172 (18.8%) as prolonged weaning patients (Figure 1).

Baseline characteristics
The clinical details of patients in the non-prolonged and prolonged weaning groups are listed in Table 1. Age, sex, and body mass index were similar between the two groups. Compared with the non-prolonged weaning group, the prolonged weaning group had higher proportions of chronic lung disease (25.0% versus 17.5%, p = 0.031) and hematologic malignancies (26.9% versus 19.2%, p = 0.032), but a lower proportion of dementia (21.5% versus 31.9%, p = 0.007). In both groups, hypoxemic respiratory failure was the most common cause of MV initiation.

Characteristics at the day of the first separation attempt
Comparison of clinical characteristics at the day of the first separation attempt is listed in Table 2. The median durations of MV before the first SBT were 5 (3–7) and 7 (4–11) days in the non-prolonged and prolonged weaning groups, respectively (p < 0.001) (Table 2). At the time of the first SBT, the proportion of tracheostomized patients in the prolonged weaning group was higher than in the non-prolonged weaning group (36.6% versus 16.8%, p < 0.001). Before SBT, 89% of the patients were receiving pressure support ventilation. The level of positive end-expiratory pressure was similar in both groups, but peak inspiratory pressure (17 cmH₂O versus 16 cmH₂O, p = 0.001) and fraction of inspired oxygen (FiO₂) (35% versus 30%, p < 0.001) were higher in the prolonged weaning group. The prolonged weaning group not only had a lower ratio of arterial oxygen partial pressure (PaO₂) to FiO₂ (257 versus 302, p < 0.001), but it also had more severe
Table 1. Clinical characteristics and outcomes.

|                                      | Non-prolonged weaning (n = 743) | Prolonged weaning (n = 172) | p-value |
|--------------------------------------|---------------------------------|-----------------------------|---------|
| Age, years                           | 67 (57–76)                      | 66 (59–73)                  | 0.317   |
| Male                                 | 485 (65.3)                      | 109 (63.4)                  | 0.637   |
| Body mass index                      | 22.5 (19.6–25.6)                | 23.1 (20.1–25.6)            | 0.650   |
| History of endotracheal intubation   | 147 (19.8)                      | 44 (25.6)                   | 0.092   |
| Comorbidities                        |                                 |                             |         |
| Chronic lung disease                 | 114 (17.5)                      | 39 (25.0)                   | 0.031   |
| Heart failure: NYHA Class III–IV     | 64 (9.8)                        | 21 (13.5)                   | 0.182   |
| Chronic renal failure                | 100 (15.3)                      | 23 (14.7)                   | 0.853   |
| Liver cirrhosis: Child–Pugh class C | 23 (3.5)                        | 6 (3.9)                     | 0.848   |
| Solid cancer                         | 280 (42.9)                      | 61 (39.1)                   | 0.383   |
| Hematologic malignancies             | 125 (19.2)                      | 42 (26.9)                   | 0.032   |
| Myopathies/neuropathies              | 68 (10.4)                       | 13 (8.3)                    | 0.434   |
| Dementia                             | 237 (31.9)                      | 37 (21.5)                   | 0.007   |
| Major reason for MV                  |                                 |                             | 0.135   |
| Hypoxemic respiratory failure        | 237 (31.9)                      | 61 (35.5)                   |         |
| Hypercapnic respiratory failure      | 197 (26.5)                      | 39 (22.7)                   |         |
| Shock                                | 185 (24.9)                      | 50 (29.1)                   |         |
| Surgery                              | 11 (1.5)                        | 5 (2.9)                     |         |
| Others*                              | 113 (15.2)                      | 17 (9.9)                    |         |
| Clinical outcomes                    |                                 |                             |         |
| Weaning success                      | 683 (91.9)                      | 77 (44.8)                   | <0.001  |
| Respiratory status at ICU discharge  |                                 |                             |         |
| No oxygen therapy                    | 156 (22.9)                      | 6 (7.8)                     | 0.002   |
| Oxygen therapy via low- or high-flow system | 521 (76.5) | 70 (90.9)                   | 0.004   |
| Non-invasive ventilation             | 7 (1.0)                         | 1 (1.3)                     | 0.826   |
| Mortality                            |                                 |                             |         |
| Intensive care unit                  | 62 (8.3)                        | 46 (26.7)                   | <0.001  |
| Hospital                             | 191 (28.9)                      | 56 (39.4)                   | 0.002   |
| Length of stay                       |                                 |                             |         |
| Intensive care unit, days            | 8 (5–11)                        | 25 (19–35)                  | <0.001  |
| Hospital, days                       | 26 (15–47)                      | 53 (36–82)                  | <0.001  |

ICU, intensive care unit; MV, mechanical ventilation; NYHA, New York Heart Association. Values are interquartile range or n (%). *Others include airway protection, neurologic impairment, and metabolic causes.
Table 2. Clinical and treatment characteristics at the day of first separation attempt.

|                                | Non-prolonged weaning (n = 743) | Prolonged weaning (n = 172) | p-value |
|--------------------------------|---------------------------------|----------------------------|---------|
| Duration of MV before first separation attempt, days | 5 [3–7] | 7 [4–11] | <0.001 |
| RASS score                     | 0.067                            |                            |         |
| RASS –1–+1                     | 537 (74.6) | 110 (67.1) |         |
| RASS < –1                      | 160 (22.2) | 44 (26.8)  |         |
| RASS > +1                      | 23 (3.2)  | 10 (6.1)   |         |
| Vital signs                    |                                  |                            |         |
| Mean arterial pressure, mmHg   | 83 (72–94) | 84 (73–93) | 0.941   |
| Heart rates, beats/min         | 89 (77–103) | 92 (80–105) | 0.147  |
| Respiratory rate, breath/min   | 18 (14–22) | 19 (15–25) | 0.010  |
| SOFA scores                    | 7 [4–9]  | 7 [5–11]   | 0.004   |
| Except respiratory system      | 5 [3–7]  | 6 [3–9]    | 0.024   |
| Type of airway                 |                                  |                            | <0.001  |
| Endotracheal tube              | 618 (83.2) | 109 (63.4) |         |
| Tracheostomy                   | 125 (16.8) | 63 (36.6)  |         |
| Setting of MV                  |                                  |                            |         |
| Mode                           |                                  |                            | 0.311   |
| Volume controlled ventilation  | 0 [0.0]  | 1 [0.6]    |         |
| Pressure controlled ventilation| 75 [10.4] | 17 [10.4]  |         |
| SIMV                           | 2 [0.3]  | 0 [0.0]    |         |
| Pressure support ventilation   | 644 [89.3] | 146 [89.0] |         |
| Peak inspiratory pressure, cmH2O | 16 [14–18] | 17 [15–20] | 0.001 |
| PEEP, cmH2O                    | 5 [5–5]  | 5 [5–5]    | 0.848   |
| Vt/PBW, ml/kg                  | 7.8 [6.2–9.8] | 7.6 [5.6–9.5] | 0.274 |
| FiO2, %                        | 30 [28–40] | 35 [30–40] | <0.001 |
| PaO2/FiO2 ratio                | 302 [233–383] | 257 [198–353] | <0.001 |
| Arterial blood gas             |                                  |                            |         |
| pH                             | 7.461 (7.429–7.497) | 7.469 (7.426–7.498) | 0.847 |
| PaCO2, mmHg                    | 34.7 [30.0–40.5] | 35.6 [30.7–44.3] | 0.067 |
| PaO2, mmHg                     | 91.0 [80.1–105.4] | 88.5 [76.6–101.7] | 0.078 |
| SaO2, %                        | 97.0 [95.8–98.2] | 96.7 [95.0–98.2] | 0.026 |

(Continued)
extrapulmonary organ dysfunction (sequential organ failure assessment score of 6 versus 5, p = 0.024). Furthermore, 15.1% of the studied patients required vasoactive drugs, and 14.8% received renal replacement therapy. Steroids were more frequently used in the prolonged weaning group (52.4% versus 43.1%, p = 0.031).

**Risk factors for prolonged weaning**

Univariable logistic regression analysis indicated that 14 variables were associated with prolonged weaning (Table 3). In multivariable analysis, the duration of MV before the first SBT (adjusted odds ratio (aOR) = 1.14, 95% CI = 1.06–1.22, p < 0.001), tracheostomy state (aOR = 1.95, 95% CI = 1.04–3.63, p = 0.036), PaO2/FiO2 ratio (aOR = 1.00, 95% CI = 0.99–1.00, p = 0.023), and use of renal replacement therapy (aOR = 2.68, 95% CI = 1.16–6.19, p = 0.021) continued to be risk factors for prolonged weaning (Table 3). In the subgroup analysis excluding the tracheostomized patients (n = 188, 20.5%), the duration of MV before the first SBT, PaO2/FiO2 ratio, and the use of renal replacement therapy were still significantly associated with prolonged weaning (Table 4).

**Discussion**

This study evaluated the clinical characteristics and outcomes of medical patients with prolonged weaning using the WIND classification and sought for the predictive factors that could be evaluated at the time of the first separation attempt from MV. We found that tracheostomy, a longer duration of MV before the first separation attempt, decreased oxygenation, and the use of renal replacement therapy were associated with increased risks of prolonged weaning. These findings were maintained after the tracheostomized patients were excluded.

Previous studies reported that the proportion of prolonged MV or prolonged weaning among patients receiving MV varied from 5% to 20% depending on the definition used in each study.5,7,8,14–16,20–22 Similarly, in this study, patients classified as prolonged weaning were common and accounted for approximately one-fifth of the patients who attempted separation from MV at least once. The prolonged MV was expected to increase, however,23 and the proportion of prolonged weaning in patients who received MV in our medical ICUs also increased by 5% compared with the proportion 5 years ago.16 Therefore, the ability to accurately identify patients who will require prolonged MV would allow clinicians to modify risk factors and improve outcomes.

We identified four patient characteristics related to prolonged weaning, one of which was the PaO2/
FiO₂ ratio. The PaO₂/FiO₂ ratio is a major parameter that represents lung function of oxygenation, which could be associated with the duration of MV in patients with acute respiratory distress syndrome.²⁴ It has not been found to be an independent risk factor for prolonged weaning or prolonged MV in the previous studies, however.¹⁰ Contrary to other studies that showed that acidosis and hypercapnia are predictors of prolonged weaning,²⁵,²⁶ no significant differences were found between the prolonged and non-prolonged weaning groups in this study. These rather intriguing findings could be attributed to the different timings of assessment between this study – which conducted evaluations at the time of recovery when MV separation was being attempted – and other studies, which conducted evaluations at the time of initiation of MV or at ICU admission.¹⁰

Second, the MV duration before the first separation attempt was associated with prolonged weaning. Because respiratory care practitioners

### Table 3. Predictors of prolonged weaning in patients who received mechanical ventilation.

|                              | Univariable OR 95% CI | p-value | Multivariable Adjusted OR 95% CI | p-value |
|------------------------------|-----------------------|---------|----------------------------------|---------|
| **Clinical characteristics** |                       |         |                                  |         |
| History of endotracheal intubation | 1.39 0.95–2.05 | 0.093  | 1.42 0.80–2.53 | 0.229  |
| Chronic lung disease         | 1.57 1.04–2.38       | 0.032  | 1.02 0.54–1.93 | 0.945  |
| Hematologic malignancies     | 1.55 1.04–2.33       | 0.033  | 1.77 0.98–3.21 | 0.059  |
| Dementia                     | 0.59 0.39–0.87       | 0.008  | 0.66 0.38–1.15 | 0.139  |
| **At the day of first separation attempt** |                       |         |                                  |         |
| MV days before first separation attempt | 1.11 1.06–1.15 | <0.001 | 1.14 1.06–1.22 | <0.001 |
| Tracheostomy state⁸          | 2.86 1.98–4.12       | <0.001 | 1.95 1.04–3.64 | 0.036  |
| **RASS score⁸**              |                       |         |                                  |         |
| RASS < −1                    | 1.34 0.91–1.99       | 0.140  | 0.75 0.40–1.41 | 0.374  |
| RASS > +1                    | 2.12 0.98–4.59       | 0.055  | 2.46 0.82–7.38 | 0.109  |
| Respiratory rate, breath/min | 1.03 1.01–1.06       | 0.008  | 0.99 0.95–1.03 | 0.631  |
| Heart rates, beats/min       | 1.01 1.00–1.02       | 0.096  | 1.01 0.99–1.02 | 0.287  |
| SOFA score except respiratory system | 1.06 1.01–1.11 | 0.013  | 0.99 0.9–1.09 | 0.911  |
| Peak inspiratory pressure, cmH₂O | 1.07 1.02–1.11 | 0.004  | 1.01 0.94–1.08 | 0.760  |
| PaO₂/FiO₂ ratio              | 1.00 0.99–1.00       | <0.001 | 1.00 0.99–1.00 | 0.023  |
| Steroid use                  | 1.45 1.03–2.04       | 0.031  | 1.06 0.65–1.73 | 0.823  |
| Renal replacement therapy    | 1.45 0.94–2.26       | 0.094  | 2.68 1.16–6.19 | 0.021  |

CI, confidence interval; FiO₂, fraction of inspired oxygen; MV, mechanical ventilation; OR, odds ratio; PaO₂, partial pressure of oxygen in arterial blood; RASS, Richmond Agitation–Sedation Scale; SOFA, sequential organ failure assessment.

⁸The reference group is endotracheal tube.

The reference group is RASS −1−1.
evaluated every patient’s readiness for SBT on a daily basis according to the standard protocol in our hospital, prolonged periods from the initiation of MV to the first separation attempt may have been affected by delayed resolution of the major cause of MV support. In addition, prolonged MV before first separation attempt may lead to the increased risk of several adverse events such as ventilator-induced lung injury and ventilator-induced diaphragmatic dysfunction, which may adversely affect successful weaning from MV.²⁷,²⁸

Third, renal failure requiring renal replacement therapy was associated with prolonged weaning. The interaction between lung and kidney is well known. Hypoxemia or hypercapnia in various lung diseases can cause kidney injury, and renal dysfunction can lead to the deterioration of lung function by causing lung edema or lung inflammation, thereby creating a vicious cycle.²⁹ In addition, acid–base imbalance accompanying renal dysfunction may increase the effort required for breathing for the compensation of metabolic acidosis, and adequate renal compensation may

| Univariable | Multivariable |
|-------------|--------------|
| Univariable | Multivariable |
| OR | 95% CI | p-value | Adjusted OR | 95% CI | p-value |
| History of endotracheal intubation | 1.39 | 0.95–2.05 | 0.093 | 1.42 | 0.81–2.52 | 0.223 |
| Chronic lung disease | 1.57 | 1.04–2.38 | 0.032 | 1.01 | 0.54–1.89 | 0.980 |
| Hematologic malignancies | 1.55 | 1.04–2.33 | 0.033 | 1.68 | 0.93–3.02 | 0.084 |
| Dementia | 0.59 | 0.39–0.87 | 0.008 | 0.69 | 0.40–1.20 | 0.190 |
| MV days before first separation attempt | 1.11 | 1.06–1.15 | <0.001 | 1.17 | 1.09–1.25 | <0.001 |
| RASS score³ | – | | | | | |
| RASS < −1 | 1.34 | 0.91–1.99 | 0.140 | 0.82 | 0.44–1.51 | 0.440 |
| RASS > +1 | 2.12 | 0.98–4.59 | 0.055 | 2.41 | 0.81–7.24 | 0.810 |
| Respiratory rate, breath/min | 1.03 | 1.01–1.06 | 0.008 | 1.00 | 0.96–1.03 | 0.832 |
| Heart rates, beats/min | 1.01 | 1.00–1.02 | 0.096 | 1.01 | 0.99–1.02 | 0.291 |
| SOFA score except respiratory system | 1.06 | 1.01–1.11 | 0.013 | 0.98 | 0.9–1.08 | 0.750 |
| Peak inspiratory pressure, cmH₂O | 1.07 | 1.02–1.11 | 0.004 | 1.01 | 0.95–1.08 | 0.706 |
| PaO₂/FiO₂ ratio | 1.00 | 0.99–1.00 | <0.001 | 1.00 | 0.99–1.00 | 0.028 |
| Steroid use | 1.45 | 1.03–2.04 | 0.031 | 1.12 | 0.69–1.83 | 0.635 |
| Renal replacement therapy | 1.45 | 0.94–2.26 | 0.094 | 2.56 | 1.12–5.89 | 0.027 |

CI, confidence interval; FiO₂, fraction of inspired oxygen; MV, mechanical ventilation; OR, odds ratio; PaO₂, partial pressure of oxygen in arterial blood; RASS, Richmond Agitation–Sedation Scale; SOFA, sequential organ failure assessment.

³The reference group is RASS −1–+1.
not be achieved for hypercapnia that occurs in lung disease.30,31 Reflecting the lung–kidney cross-talk, several studies have also indicated that renal dysfunction is a risk factor for prolonged weaning.25,32,33

Finally, we found that tracheostomy status at the first separation attempt was also associated with prolonged weaning. Tracheostomy is often considered in patients perceived to be difficult to wean.34 In this study, although we could not obtain data on the cause of tracheostomy, tracheostomy was considered when the patients were expected to need artificial airways, such as for insufficient ability to clear secretion or for prolonged MV. Kollef et al.35 showed that the duration of MV was longer in patients who underwent tracheostomy at the physician’s discretion compared with patients who did not receive a tracheostomy, suggesting that physicians have the ability to select patients for whom prolonged weaning can be predicted. Therefore, we analyzed the subgroup after the exclusion of tracheostomized patients to confirm risk factors for prolonged weaning; however, the remaining three factors were still significantly associated with an increased risk of prolonged weaning.

This study has contributed to the research on predictive factors associated with an increased risk of prolonged weaning using the WIND classification; however, there are several limitations that should be acknowledged. First, the significance of our findings might have been influenced by the inherent selection bias of this observational study. The data were collected prospectively from all the consecutive patients who had been admitted to the medical ICU from patients who were on MV support for more than 24h and who were screened daily for weaning readiness based on the standardized weaning protocol, however. Although patients were primarily managed by attending physicians with responsibility for patient care, the weaning process and general care in the ICU were provided based on the institutional protocols and general guidelines. In addition, we used multivariable regression model to control for potential confounders. The possible existence of bias owing to unmeasured risk factors remains, however. Second, this study was conducted at a single institution with a protocol-based weaning program, which may limit the generalizability of our findings to other centers in which no specific programs are available for weaning. Third, tracheostomy was performed in one-fifth of patients, which is higher than the rates (11–15%) in an international multicenter study36 and may improve aspects of care of patients on MV.37 Subgroup analysis (excluding the tracheostomized patients) revealed that the remaining three factors were associated with increased risks of prolonged weaning, however.

In conclusion, longer duration of MV before weaning trials, tracheostomy status, poor oxygenation, and need for renal replacement therapy at the time of the first separation attempt of MV could be predictive for prolonged weaning. Further studies should be conducted to identify risk factors for prolonged weaning in patients with various respiratory pathophysiologies and extrapulmonary medical conditions to establish treatment strategies to improve the clinical outcomes and reduce the socioeconomic burden of prolonged weaning, however.

Declarations

Ethics approval and consent to participate
The institutional review board of the Samsung Medical Center approved this study and waived the requirement for informed consent because of the observational nature of the study.

Consent for publication
Not applicable.

Author contributions
Soo Jin Na: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Ryoung-Eun Ko: Formal analysis; Investigation; Methodology; Validation; Writing – review & editing.

Jimyoung Nam: Data curation; Investigation; Resources; Writing – review & editing.

Myeong Gyun Ko: Data curation; Investigation; Resources; Writing – review & editing.

Kyeongman Jeon: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

Acknowledgements
None.
Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Samsung Medical Center grant (SMO1180151) and the Korean Society of Critical Care Medicine (2019).

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID iD
Kyeongman Jeon  https://orcid.org/0000-0002-4822-1772

Supplemental material
Supplemental material for this article is available online.

References
1. Wunsch H, Wagner J, Herlim M, et al. ICU occupancy and mechanical ventilator use in the United States. Crit Care Med 2013; 41: 2712–2719.
2. Lone NI and Walsh TS. Prolonged mechanical ventilation in critically ill patients: epidemiology, outcomes and modelling the potential cost consequences of establishing a regional weaning unit. Crit Care 2011; 15: R102.
3. Kahn JM, Le T, Angus DC, et al. The epidemiology of chronic critical illness in the United States. Crit Care Med 2015; 43: 282–287.
4. Cox CE, Carson SS, Lindquist JH, et al. Differences in one-year health outcomes and resource utilization by definition of prolonged mechanical ventilation: a prospective cohort study. Crit Care 2007; 11: R9.
5. Jeong BH, Ko MG, Nam J, et al. Differences in clinical outcomes according to weaning classifications in medical intensive care units. PLoS ONE 2015; 10: e0122810.
6. Damuth E, Mitchell JA, Bartock JL, et al. Long-term survival of critically ill patients treated with prolonged mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med 2015; 3: 544–553.
7. Hill AD, Fowler RA, Burns KE, et al. Long-term outcomes and health care utilization after prolonged mechanical ventilation. Ann Am Thorac Soc 2017; 14: 355–362.
8. Lee HW and Cho YJ. The impact of mechanical ventilation duration on the readmission to intensive care unit: a population-based observational study. Tuberc Respir Dis 2020; 83: 303–311.
9. Rose L, McGinlay M, Amin R, et al. Variation in definition of prolonged mechanical ventilation. Respir Care 2017; 62: 1324–1332.
10. Ghauri SK, Javaeed A, Mustafa KJ, et al. Predictors of prolonged mechanical ventilation in patients admitted to intensive care units: a systematic review. Int J Health Sci 2019; 13: 31–38.
11. MacIntyre NR, Epstein SK, Carson S, et al. Management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. Chest 2005; 128: 3937–3954.
12. Jeon K. Expanding use of the ProVent score. Tuberc Respir Dis 2019; 82: 173–174.
13. Burns KEA, Rizvi L, Cook DJ, et al. Ventilator weaning and discontinuation practices for critically ill patients. JAMA 2021; 325: 1173–1184.
14. Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. Eur Respir J 2007; 29: 1033–1056.
15. Béduneau G, Pham T, Schortgen F, et al. Epidemiology of weaning outcome according to a new definition. The WIND study. Am J Respir Crit Care Med 2017; 195: 772–783.
16. Jeong BH, Lee KY, Nam J, et al. Validation of a new WIND classification compared to ICC classification for weaning outcome. Ann Intensive Care 2018; 8: 115.
17. Lago AF, Gastaldi AC, Mazzoni AAS, et al. Comparison of International Consensus Conference guidelines and WIND classification for weaning from mechanical ventilation in Brazilian critically ill patients: a retrospective cohort study. Medicine 2019; 98: e17534.
18. Jeon K, Jeong BH, Ko MG, et al. Impact of delirium on weaning from mechanical ventilation in medical patients. Respir Care 2016; 21: 313–320.
19. Subirà C, Hernández G, Vázquez A, et al. Effect of pressure support vs T-Piece ventilation strategies during spontaneous breathing trials on successful extubation among patients receiving mechanical ventilation: a randomized clinical trial. *JAMA* 2019; 321: 2175–2182.

20. Funk GC, Anders S, Breyer MK, et al. Incidence and outcome of weaning from mechanical ventilation according to new categories. *Eur Respir J* 2010; 35: 88–94.

21. Pu L, Zhu B, Jiang L, et al. Weaning critically ill patients from mechanical ventilation: a prospective cohort study. *J Crit Care* 2015; 30: 862.e7–862.e13.

22. Nagata I, Takei T, Hatakeyama J, et al. Clinical features and outcomes of prolonged mechanical ventilation: a single-center retrospective observational study. *J A Clin Rep* 2019; 5: 73.

23. Zilberberg MD, de Wit M and Shorr AF. Accuracy of previous estimates for adult prolonged acute mechanical ventilation volume in 2020: update using 2000–2008 data. *Crit Care Med* 2012; 40: 18–20.

24. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; 307: 2526–2533.

25. Clark PA, Inocencio RC and Lettieri CJ. I-TRACH: validating a tool for predicting prolonged mechanical ventilation. *J Intensive Care Med* 2018; 33: 567–573.

26. Clark PA and Lettieri CJ. Clinical model for predicting prolonged mechanical ventilation. *J Crit Care* 2013; 28: 880.e1–880.e7.

27. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002; 122: 2115–2121.

28. Hortal J, Giannella M, Perez MJ, et al. Incidence and risk factors for ventilator-associated pneumonia after major heart surgery. *Intensive Care Med* 2009; 35: 1518–1525.

29. Husain-Syed F, Slutsky AS and Ronco C. Lung-kidney cross-talk in the critically ill patient. *Am J Respir Crit Care Med* 2016; 194: 402–414.

30. Huang CC, Tsai YH, Lin MC, et al. Respiratory drive and pulmonary mechanics during haemodialysis with ultrafiltration in ventilated patients. *Anaesth Intensive Care* 1997; 25: 464–470.

31. Madias NE. Renal acidification responses to respiratory acid-base disorders. *J Nephrol* 2010; 23: S85–S91.

32. Vieira JM Jr, Castro I, Curvello-Neto A, et al. Effect of acute kidney injury on weaning from mechanical ventilation in critically ill patients. *Crit Care Med* 2007; 35: 184–191.

33. Pan SW, Kao HK, Lien TC, et al. Acute kidney injury on ventilator initiation day independently predicts prolonged mechanical ventilation in intensive care unit patients. *J Crit Care* 2011; 26: 586–592.

34. Cox CE, Carson SS, Holmes GM, et al. Increase in tracheostomy for prolonged mechanical ventilation in North Carolina, 1993–2002. *Crit Care Med* 2004; 32: 2219–2226.

35. Kollef MH, Ahrens TS and Shannon W. Clinical predictors and outcomes for patients requiring tracheostomy in the intensive care unit. *Crit Care Med* 1999; 27: 1714–1720.

36. Esteban A, Frutos-Vivar F, Muriel A, et al. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med* 2013; 188: 220–230.

37. Nieszkowska A, Combes A, Luyt CE, et al. Impact of tracheotomy on sedative administration, sedation level, and comfort of mechanically ventilated intensive care unit patients. *Crit Care Med* 2005; 33: 2527–2533.