Original Article

Independent Risk Factors of Failed Extubation among Adult Critically Ill Patients: A Prospective Observational Study from Saudi Arabia

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Abstract

Background: Mechanical ventilation provides essential support for critically ill patients in several diagnoses; however, extubation failure can affect patient outcomes. From Saudi Arabia, no study has assessed the factors associated with extubation failure in adults.

Methods: This prospective observational study was conducted in the intensive care unit of a tertiary care hospital in Riyadh, Saudi Arabia. Adult patients who had been mechanically ventilated via the endotracheal tube for a minimum of 24 hours and then extubated according to the weaning protocol were included. Failed extubation was defined as reintubation within 48 hours of extubation.

Results: A total of 505 patients were included, of which 72 patients had failed extubation (14.3%, 95% CI: 11.4%–17.7%). Compared with the failed extubation group, the successfully extubated group had significantly shorter duration of mechanical ventilation (mean difference: -2.6 days, 95% CI: -4.3 to -1; $P = 0.001$), a slower respiratory rate at the time of extubation (mean difference: -2.3 breath/min, 95% CI: -3.8 to -1; $P = 0.0005$), higher pH (mean difference: 0.02, 95% CI: 0.001–0.04; $P = 0.03$), and more patients with strong cough (percent difference: 17.7%, 95% CI: 4.8%–30.5%; $P = 0.02$). Independent risk factors of failed extubation were age (aOR = 1.02; 95% CI: 1.002–1.03; $P = 0.03$), respiratory rate (aOR = 1.06, 95% CI: 1.01–1.1; $P = 0.008$), duration of mechanical ventilation (aOR = 1.08, 95% CI: $1.03 - 1.1$; $P < 0.001$), and pH (aOR = 0.02, 95% CI: 0.0006–0.5; $P = 0.02$).

Conclusion: Older age, longer duration of mechanical ventilation, faster respiratory rate, and lower pH were found to be independent risk factors that significantly increased the odds of extubation failure among adults.

Keywords: Adverse effects, airway extubation, critically ill, mechanical ventilation, reintubation, risk factors

INTRODUCTION

Mechanical ventilation (MV) provides essential support for a myriad of diagnoses in critically ill patients including acute respiratory failure.[1] However, invasive MV can result in serious complications, such as ventilator-associated pneumonia, lung injury, and airway trauma, and also in

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death. The risks of adverse events increase with increased duration of ventilator dependence.[2,3] Clinicians need to delicately balance between mitigating the risks associated with delayed and premature extubation, as both can lead to significantly poor outcomes.[1]

Extubation failure is defined as an inability to sustain spontaneous breathing after the removal of the artificial airway, and the need to reintubate within a specified time period, usually 24–72 hours after extubation.[4] Several risk factors of extubation failure have been identified, some of which are related to the demographics and clinical condition of the patient such as having a medical diagnosis,[5] older age, duration of ventilator support,[6] and higher acute physiology and chronic health evaluation (APACHE) II scores.[7] Other predictors of failed extubation are related to weaning parameters, such as maximal inspiratory pressure, maximal expiratory pressure, minute ventilation, tidal volume, and rapid shallow breathing index (RSBI).[8] To maximize the likeliness of successful extubation, several criteria should be achieved, such as the ability to protect airway, strong respiratory muscles, hemodynamic stability, and minimal ventilator support parameters,[9,10] in addition to screening for high risk of extubation failure.[11]

In Saudi Arabia, there is paucity of studies regarding factors associated with extubation failure in adults. Therefore, this study was conducted with the aim of identifying risk factors of extubation failure in the setting of a tertiary referral hospital in Saudi Arabia, under the hypothesis that the risk factors will mostly be in agreement with those reported internationally.

MATERIALS AND METHODS

Study design, setting, and patients
This prospective observational study was conducted in the intensive care unit (ICU) of King Saud Medical City (KSMC), Riyadh, Saudi Arabia, between January 1 and June 30, 2023. KSMC is the largest tertiary referral hospital in the central region of Saudi Arabia, with its ICU having 120 beds and an average monthly admission of 280 patients. All ICU beds are fully equipped with capabilities of invasive and noninvasive monitoring and ventilation. The ICU is operated by attending intensivists round the clock, with a nurse-to-patient ratio of 1:1, and a respiratory therapist-to-patient ratio of 1:8.

Patients were included if they were aged ≥18 years (no upper age limit), had been mechanically ventilated via the endotracheal tube, with a minimum MV duration of 24 hours, and had been extubated in accordance with the weaning protocol of the ICU and with the agreement of the treating consultant. We only included the primary episode of weaning and extubation; therefore, if a patient was extubated and then reintubated, the second attempt of weaning and extubation was not included in the study to maintain independence of data.

Patients were excluded if they had been mechanically ventilated via the tracheostomy tube, experienced unplanned extubation (self-extubation), MV via endotracheal tube was converted to tracheostomy tube directly, without a period of spontaneous breathing, and if they were fast-track patients who were kept intubated postoperatively or were transported to the ICU for a short period of close monitoring.

Sample size calculation
Based on our historical extubation failure rate of 15%, the sample size was estimated to be 503 patients to detect an odds ratio of 1.5 with a 90% power at a type I error rate of 5%. However, all eligible patients within the study period were enrolled in the study.

Operational definitions
For the purpose of this study, extubation was defined as a planned extubation that was intentionally carried out by the respiratory therapist after evaluation of patients' readiness, and assessment as per the ICU weaning protocol, and with agreement of the treating consultant. Failed extubation was defined as the need of reintubation and MV within 48 hours of extubation, as judged by the treating consultant.[12] The current study was observational, as reintubation was entirely at the discretion of the treating consultant.

Study outcomes
The primary outcome was identification of independent risk factors of failed extubation among sociodemographic, clinical, or ventilation-related variables (see data management section). The secondary outcomes were determining the failed extubation rate calculated as the proportion of patients who required reintubation within 48 hours of extubation (of all extubated). In addition, the study compared the demographic and clinical characteristics between patient groups with successful and failed extubations.

Patients' management and extubation process
In our ICU, weaning and extubation is a multidisciplinary protocolized process. It involves a spontaneous breathing trial (SBT) (while still ventilated) when deemed fit by the treating team. Patients who successfully pass the SBT are assessed according to our weaning protocol that

entails multiple oxygenation and ventilation parameters, arterial blood gases evaluation, review of the chest X-ray, hemodynamic stability, respiratory rate, strength of cough, and cuff-leak test. However, the treating team's decision to extubate may override the conclusion of the weaning protocol's assessment. All patients were extubated to noninvasive ventilation as a routine practice [Supplementary Tables 1–5].

In our ICU, sedation of ventilated patients follows a nurse-driven protocol to achieve a predefined target Richmond Agitation Sedation Scale score. The protocol encourages light sedation unless dictated otherwise by the patient's condition (such as in brain-protective strategy), and utilizes non-benzodiazepine sedatives, fentanyl, and propofol. Neuromuscular blocking agents are discouraged unless strictly necessary and by order of the treating consultant. Nutrition of critically ill patients is managed by clinical dieticians, who aim to initiate enteral feeding as soon as possible, reaching at least 60% of the nutritional requirements within 2–3 days.

Data management

An attending respiratory therapist filled out a sheet at the time of the extubation, from which the following variables were recorded: age, duration of MV, APACHE 4 score, respiratory rate (count/minute), inspired tidal volume (ml), RSBI (calculated as respiratory rate divided by tidal volume in ml), pressure support provided (cmH$_2$O), oxygen fraction of inspired oxygen (FiO$_2$), arterial blood gases including: pH, arterial partial pressure of oxygen (PaO$_2$), arterial partial pressure of carbon dioxide (PaCO$_2$), bicarbonate level (HCO$_3$), and peripheral oxygen saturation. We also recorded the assessment of the respiratory therapist on the strength of cough (as weak, moderate, or strong), ability of the patient to generate a negative inspiratory force (NIF) of less than −20 cmH$_2$O, positive or negative cuff leak test, and if the patient was reintubated within 48 hours from extubation.

All variables were recorded in an online Google Sheet prepared for the purpose of the study. Data collectors were trained to extract the required variables from the extubation sheet at the specific time of extubation. To ensure quality and completeness of data, a copy of the extubation sheet was compared with the entered data by the primary investigator.

Ethical considerations

The study was approved by the Institutional Review Board of KSMC. Requirement for a separate informed consent was waived by the IRB owing to the observational study design and by requirement of complying with the Declaration of Helsinki, 2013. No patients' identifiers were recorded, instead patients were assigned a study code. Access to the Google sheet was granted only to the data collectors and the primary investigator. The confidentiality of the collected data were strictly maintained, and the raw data would securely be available only with the primary investigator for 2 years after the study has been published.

Statistical analysis

Being a prospective study, no data were missing for all enrolled patients. Continuous variables were summarized as mean ± standard deviation (SD) and were between group comparison (i.e., successful vs. and failed extubation groups) by Student *t*-test if the data fulfilled the normality assumption, otherwise the non-parametric alternative (Wilcoxon rank sum test) was used. Categorical variables were summarized as frequency (count) and percentage, and compared between groups by Pearson's Chi-square test, or Fisher's exact test if any cell in the contingency 2 × 2 table had a value <4. Group comparisons were presented as mean or percent difference, along with the corresponding 95% confidence interval (CI) and *P* value. There was no correction for multiple testing, and thus, results of group comparisons should be interpreted cautiously.

For the purpose of identification of independent risk factors of extubation failure, we fitted a multivariable logistic regression model, where all collected data variables were initially entered in the model, and using the backward elimination, the model retained variables with *P* values <0.1. Results were presented as adjusted odds ratio (aOR). We evaluated the assumptions of logistic regression including absence of multicollinearity of continuous variables using Spearman's correlation, and linearity of independent variables and logit outcome using Box-Tidwell test. Goodness of fit of the model was assessed by Hosmer–Lemeshow test (considered well fitted if *P* value >0.05), and variance inflation factors (VIF) <4. A calibration belt of the predictive ability of the model was constructed at the 80% and 95% confidence levels.

All statistical tests were two tailed, and a *P* value <0.05 was considered statistically significant. STATA version 17 was used for statistical analyses (Stata Corp. LLC, College Station, TX:USA).

RESULTS

During the study period, 505 patients were included after the exclusion of 264 patients for various reasons [Figure 1]. Of these, 72 patients had a failed extubation (14.3%, 95% CI: 11.4% to 17.7%). The enrolled patients had a mean

age of 47.2 ± 19.1 years, included 96 (19%) females, were mechanically ventilated for an average duration of 6.5 ± 5.7 days, and had an average APACHE IV score of 21.6 ± 5.6. Figure 2 depicts the different indications of intubation and percentages in each group, and there was no association with extubation failure (Chi-square $P = 0.97$).

Compared with the failed extubation group, patients in the successful extubation group had significantly fewer MV days ($P = 0.001$), slower respiratory rate ($P = 0.0005$), lower RSBI ($P < 0.001$), higher pH ($P = 0.03$), and more patients with strong cough ($P = 0.02$) [Table 1]. Notably, three types of extubation protocol violations occurred and were overridden by the treating consultant, namely, NIF higher than −20 cmH$_2$O, positive cuff leak test, and extubation with weak cough. However, there were no significant differences in their percentages in both groups [Supplementary Table 6].

Independent risk factors of failed extubation

Using the backward elimination method, the following four variables were retained in the logistic regression model: age (aOR: 1.02, 95% CI: 1.002–1.03; $P = 0.03$), duration of MV (aOR: 1.08, 95% CI: 1.03–1.1; $P < 0.001$), respiratory rate (aOR: 1.06, 95% CI: 1.01–1.1; $P = 0.008$), and pH (aOR: 0.017, 95% CI: 0.0006–0.5; $P = 0.02$) [Table 2]. The model satisfied all assumptions of logistic regression, it was well fitted with Hosmer–Lemeshow P value = 0.09, and all predictors had VIFs <4 [Supplementary Tables 7-9]. The model correctly classified 85% of the cases, and the calibration belt shows that the prediction ability was statistically different from perfect prediction at both 80% and 95% confidence levels [Figure 3].

DISCUSSION

In this prospective observational study, the extubation failure rate was 14.3%, and we identified the independent risk factors of extubation failure to be higher age, longer duration of MV, faster respiratory rate, and lower pH. The extubation failure rate falls within the usually reported range of 10%–20%,[13] and is comparable with the 13.5% failure rate reported by a recent case–control study.[14]

The primary outcome of the study indicates that controlling for all other variables, as an age increase by 1 year, an respiratory rate at the time of extubation increase by 1 breath/minute, or a 1-day longer duration of MV increases the odds of extubation failure by 2%, 6%, and 8% respectively. In contrast, an increase in pH by 1 is a protective exposure, as it lowers the odds of extubation failure by 98%.
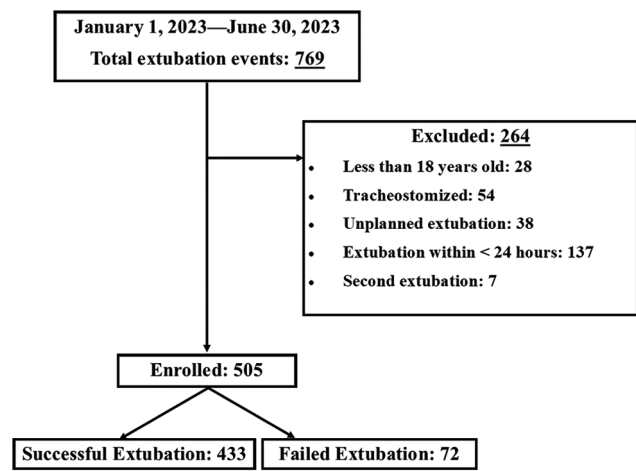

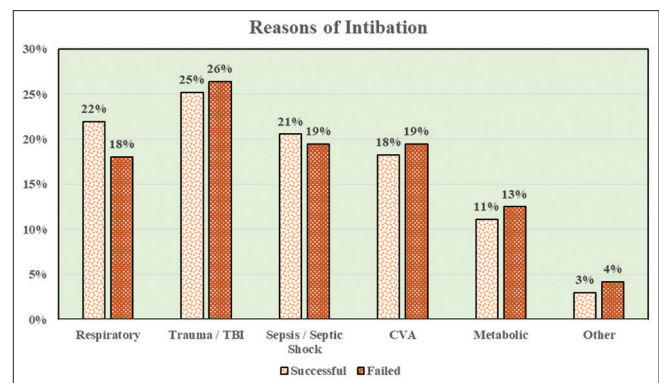**Figure 1:** Patients' enrollment flow diagram

Figure 2: Intubation indications in the study groups. TBI – traumatic brain injury; CVA – cerebrovascular accident; "Other" includes intoxication, burn, seizures, and upper gastrointestinal bleeding. Chi-square test of association: $P = 0.97$
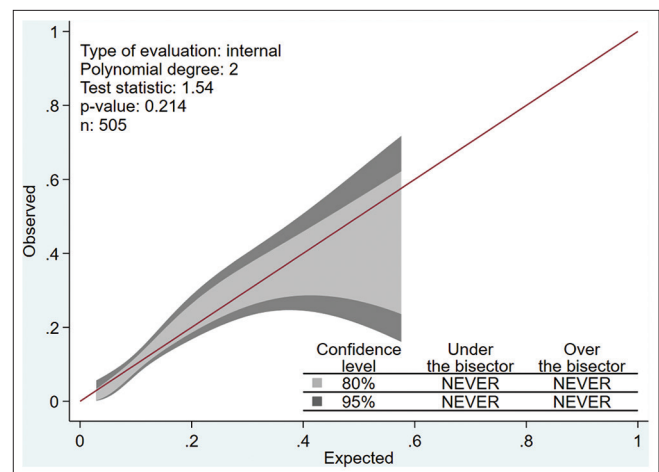

Figure 3: Calibration belt of logistic regression predictive ability

These findings seem comprehensible within the context of a critically ill patient. With advancing age, a decline in respiratory system functionality and respiratory muscles' strength could be expected, putting older patients at risk of extubation failure,[15] and indeed, evidence suggest that

Table 1: Demographic and clinical characteristics of the study groups

Variable	Successful extubation (*n*=433)	Failed extubation (*n*=72)	Mean/percent difference; 95% CI	*P*
Age (years), mean±SD	46.7±19	50.7±19.7	−4 (−9–1)	0.1
Sex (female), *n* (%)	81 (18.7)	15 (20.8)	−2.1 (−12.2–7.9)	0.7
APACHE 4 (mean±SD)	21.6±5.6	20.8±5.7	0.8 (−0.6–2.2)	0.3
MV days	6.2±5.4	8.8±6.8	−2.6 (−4.3–−1)	0.001
IBW (kg)	64.5±10.1	62.4±10.9	2 (−0.7–4.8)	0.2
ETT ID (mm)	7.8±7.9	7.4±0.3	0.4 (−0.4–1.1)	0.7
FiO_2	0.3±0.05	0.3±0.06	−0.003 (−0.02–0.01)	0.8
RR (breath/min)	18±5.7	20.3±6	−2.3 (−3.8–−1)	0.0005
TV (mL)	513±136	489±126	24 (−8.4–56.2)	0.06
RSBI	38.7±20.5	44.8±18.1	−6.1 (−11.2–−1.1)	<0.001
PEEP (cmH_2O)	6±1.4	6.3±1.5	−0.3 (−0.6–0.1)	0.2
pH	7.4±0.07	7.4±0.08	0.02 (0.001–0.04)	0.03
$PaCO_2$ (mmHg)	38.3±6.5	38.9±10	−0.6 (−3–1.9)	0.7
PaO_2 (mmHg)	90±26.7	85±27.4	5 (−2–11.9)	0.3
HCO_3 (mEq/L)	25.3±4.6	25.1±4.8	0.3 (−0.9–1.5)	0.8
SpO_2%	95.2±9.7	94.6±8.6	1 (−2–3)	0.4
Positive cuff leak test, *n* (%)	31 (7.2)	3 (4.2)	3 (−2.2–8.2)	0.3
NIF <−20 (cmH_2O), *n* (%)	383 (88.5)	58 (80.6)	7.9 (−1.7–17.5)	0.1
Cough strength				
Weak	34 (7.8)	8 (11.1)	3.3 (−3.6–13.2)	0.02
Moderate	112 (25.9)	29 (40.3)	14.4 (2.2–27.3)	
Strong	287 (66.3)	35 (48.6)	17.7 (4.8–30.5)	

Wilcoxon rank-sum test used for all continuous variable's comparisons. MV – mechanical ventilation; IBW – Ideal body weight; ETT – Endotracheal tube; ID – internal diameter; FiO_2 – Fraction of inspired oxygen; RR – Respiratory rate; TV – Tidal volume; RSBI – Rapid Shallow Breathing Index; PEEP – Positive end expiratory pressure; pH – Potential of hydrogen; $PaCO_2$ – Arterial partial pressure of carbon dioxide; PaO_2 – Arterial partial pressure of oxygen; SpO_2 – Oxygen saturation; NIF – Negative inspiratory force; APACHE – Acute physiology and chronic health evaluation; SD – Standard deviation; CI – Confidence interval

Table 2: Multivariable logistic regression model

Variable	aOR (95% CI)	*P*
Age (years)	1.02 (1.002–1.03)	0.03
RR (bpm)	1.06 (1.01–1.1)	0.008
MV (days)	1.08 (1.03–1.1)	<0.001
pH	0.02 (0.0006–0.5)	0.02

No records excluded for missing data. MV – Mechanical ventilation; bpm – Breath per min; pH – Potential of hydrogen; CI – Confidence interval; aOR – Adjusted odds ratio; RR – Respiratory rate

elderly patients are exposed to higher rates of extubation failure compared with the general population.[16] Rapid respiratory rate at the time of extubation could also be a culprit of extubation failure, as it is usually ends in respiratory muscles' fatigue that may eventually lead to respiratory failure and the need to reinstitute mechanical ventilation.[17] It logically follows that a lower pH may be a sign of respiratory muscle weakness, and suboptimal breathing rate and depth, thereby contributing to the risk of extubation failure. Gobert *et al.*[18] argue that higher pH may reflect ventilation capacity, and thus, may be considered protective against extubation failure. Prolonged mechanical ventilation has been identified as a risk factor of developing ICU-acquired weakness, which commonly affects the respiratory muscles, thereby contributing to an increased risk of extubation failure.[19]

The results of this study, although relatively new in the Saudi population, are in concordance with worldwide findings. A recent systematic literature review and meta-analysis[20] identified older age, prolonged MV, and low pH as risk factors of extubation failure. In another Bayesian meta-analysis, both age and duration of MV were significant predictors of extubation failure.[21] Zhao *et al.*[22] constructed a machine learning model on data from the Medical Information Mart for Intensive Care (MIMIC-IV), and the best performing model with an area under the receiver operator characteristic curve of 0.835 included all the four predictors identified in our study.

Findings of this study support our initial hypothesis and the notion that predictors of extubation failure within our setting in Saudi Arabia are not different from those identified internationally, perhaps, because the nature of the disease or condition is what dictates these risk factors, rather than the population's ethnic characteristics. The results of this study should provide more confidence to clinicians working within the setting of Saudi Arabia to implement American or European evidence-based recommendations on the Saudi population. The identified four risk factors in this study should be given special attention by clinicians when considering extubation or when screening for high-risk patients of extubation failure. Experts and policymakers may need to consider those four factors when formulating local extubation protocols or guidelines. Undoubtedly, further investigations are warranted to establish conclusive evidence, possibly with a larger cohort from multiple centers, including more

detailed data and variables, and using more rigorous analysis techniques such as propensity score matching.

Limitations

This study is subject to the inherent limitations within the observational design. In addition, being a single center study, it reflects management within our hospital and affects its external validity, especially that our practice of post-extubation noninvasive ventilation is not universally adopted. Although we enrolled the predefined sample size, the odds ratios of the significant predictors did not reach the values we had estimated for effect size (OR = 1.5), and thus, the study may be underpowered. In this study, comorbidities were not evaluated as risk factors, although generally, the different disease categories were not associated with extubation failure, and the APACHE IV scores (which incorporates comorbidities) were not different between groups. Many laboratory investigations were identified as predictors of extubation failure by others,[20] but we did not evaluate any due to feasibility issues, as our source of data collection was the extubation sheet of the respiratory therapists.

CONCLUSION

In this study, older age, longer duration of mechanical ventilation, higher respiratory rate, and lower pH values were found to be significant risk factors of extubation failure within 48 hours of extubation among adult patients who had been mechanically ventilated for at least 24 hours. These factors should be given special attention when considering extubation attempts and should be assigned greater importance in extubation protocols.

Ethical considerations

The study was approved by the Institutional Review Board of KSMC (Ref. no.: H1RI-10-Oct22-02). Requirement for a separate patient consent was waived owing to the observational study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: A.H.A.A., M.A.A.O., and W.T.A; Methodology: K.A.A., P.R.J., A.P.L., and N.H.S.; Data analysis: W.T.A.; Writing–original draft preparation: W.T.A.,

A.A., and A.Y.A.; Writing – review and editing: All Authors; Supervision: A.H.A.A. and M.A.A.O.

All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Daily screening

All ventilated patients will be assessing by the RT daily between 7:30 am to 9:30 am (excluding: Patients on septic shock protocol - brain protective strategy - specific order by the treating consultant)
The RT will ensure that the patient meets the following baseline criteria before initiating the SBT
  Evidence for some reversal of the underlying cause of respiratory failure
  Adequate oxygenation (PaO_2/FiO_2=150/200; PEEP 5/8 cm H_2O; FiO_2 ≤0.4/0.5 and PH ≥7.25)
  Hemodynamic stability is defined as the absence of active myocardial ischemia and the absence of clinically important hypotension (i.e., a condition requiring no vasopressor therapy or therapy with only low-dose vasopressors such as dopamine or dobutamine <5 mcg/kg/min)
  Temperature <38°C
  Hemoglobin 8–10 g/dL
  GCS <8
  The capability to initiate an inspiratory effort

RT – Respiratory therapist; SBT – Spontaneous breathing trial; PEEP – Positive end expiratory pressure; pH – Potential of hydrogen; PaO_2 – Arterial partial pressure of oxygen; FiO_2 – Fraction of inspired oxygen; GCS: Glasgow Coma Scale

Supplementary Table 2: Spontaneous breathing trial

SBT can only be initiated if all criteria of daily screening are met
CPAP of 5 cm H_2O and pressure support ≤8 cm H_2O
Note: For patients with endotracheal tube diameter <8.0, consider higher pressure support to compensate for increase airway resistance
The initial 10 min of SBT should be monitored closely, before a decision is made to continue (this is often referred to as the screening phase of an SBT). Thereafter, the patient should continue the trial for at least 30–120 min
If the patient experience any of the following during the trial, immediately return patient to the previous ventilator settings and notify the attending physician
  RR >35 bpm or change in RR >50% above baseline, for >5 min
  RSBI >105
  SpO_2 <90%, PaO_2 <50 mmHg, increase in $PaCO_2$ >10 mmHg from the baseline
  HR >140 bpm or sustained increase or decrease in HR of >20%
  Systolic blood pressure >180 mmHg or <90 mmHg
  Change in mental state
  Dyspnea
  Use of accessory muscles, signs of increased WOB
  Onset of anxiety and diaphoresis

RR – Respiratory rate; RSBI – Rapid shallow breathing index; HR – Heart rate; $PaCO_2$ – Arterial partial pressure of carbon dioxide; PaO_2 – Arterial partial pressure of oxygen; SpO_2 – Oxygen saturation; SBT – Spontaneous breathing trial; CPAP – Continuous positive airway pressure; bpm – Breath per min; WOB –Work of breathing

Supplementary Table 3: Extubation process

If the patient passes SBT, the following extubation criteria must be checked
  Adequate cough
  Ability to protect the airway
  Positive cuff leak test
  NIF >20
Cuff leak test can be detected in any of the following
  Qualitative assessment: Is performed by deflating the cuff and then listening for air movement around the ETT using a stethoscope place over the trachea
  Quantitative assessment: Is performed by deflating the ETT cuff and measuring the difference between the inspired and expired TVs of ventilator-delivered breaths during volume-cycled mechanical ventilation. The lowest three expired TVs obtained over six breaths are averaged and then subtracted from the inspired TV to give the cuff leak volume. Cuff leak volumes <110 mL or <12%–24% of the delivered TV have been suggested as thresholds for determining whether airway patency may be diminished
If extubation criteria are met, or the treating consultant opts to over-ride, a clear written physician order will be obtained before extubation
Initiate NIV according to protocol
The RT monitors the patient within 48 h of extubation for any of the following
  Increase WOB
  GCS
  Vital signs
  Increase FiO_2 requirements
  Immobilization of secretion

SBT – Spontaneous breathing trial; RT – Respiratory therapist; NIF – Negative inspiratory force; ETT – Endotracheal tube; FiO_2 – Fraction of inspired oxygen; NIV – Noninvasive ventilation; TV – Tidal volume; GCS – Glasgow Coma Scale; WOB – Work of breathing

Supplementary Table 4: Postextubation noninvasive support

NIV to be delivered continuously immediately after extubation using bi-level positive-airway pressure mode, for a scheduled 24 h
Inspiratory positive-airway pressure to be adjusted according to patient's tolerance (12–20 cm H_2O)
Expiratory positive airway pressure at 5–6 cm H_2O
FiO_2 was set to achieve arterial O_2 saturation by pulse-oximetry of >92%
The position of the head of the bed was kept at 45° if applicable
NIV could be interrupted for eating and drinking, for 15–20 min
The facial skin is assessed every 4 h to prevent damage from the tightly fitting face mask used to deliver the ventilation
NIV is applied to achieve a target RR <25/min
Clinical monitoring: HR, RR, blood pressure and appearance of respiratory distress such as the use of accessory muscles of respiration
NIV is discontinued in case of inability to tolerate the mask because of discomfort, deterioration in ventilatory parameters (rise in PCO_2, fall in pH or PaO_2), deteriorating state of consciousness or hemodynamic instability. Treating physician informed

RR – Respiratory rate; HR – Heart rate; PaO_2 – Arterial partial pressure of oxygen; NIV – Noninvasive ventilation; FiO_2 – Fraction of inspired oxygen

Supplementary Table 5: Re-intubation criteria

The decision to re-intubate is a multidisciplinary decision, but ultimately falls under the responsibility of the treating consultant/designee
Immediate reintubation when any of the following major clinical events were present
    Respiratory or cardiac arrest
    Respiratory pauses with loss of consciousness or gasping for air
    Psychomotor agitation inadequately controlled by sedation
    Massive aspiration
    Persistent inability to remove respiratory secretions
    HR below 50/min, with loss of alertness
    Severe hemodynamic instability without response to fluids and vasoactive drugs
Development of respiratory failure
    Respiratory acidosis (arterial pH of 7.35 or less with $PaCO_2$ of 45 mmHg or more)
    Arterial O_2 saturation by pulse oximetry <90% or PaO_2 <60 mmHg at an inspired O_2 fraction of 0.5 or more
    Respiratory frequency exceeding 35/min
    Decreased consciousness, agitation, or diaphoresis
    Clinical signs suggestive of respiratory muscle fatigue and/or increased work of breathing, such as the use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces
Re-intubation is not considered only in the case of a valid do not intubate order, according to policy

HR – Heart rate; PaO_2 – Arterial partial pressure of oxygen; $PaCO_2$ – Arterial partial pressure of carbon dioxide

Supplementary Table 6: Protocol violations among the study groups

Variable	Successful extubation (*n*=433), *n* (%)	Failed extubation (*n*=72), *n* (%)	Percent difference (95% CI); *P*
NIF >−20 cm H_2O	50 (11.5)	14 (19.4)	7.9 (−1.1–19.3); 0.09
Positive cuff-leak test	31 (7.2)	3 (4.2)	3 (−4.9–7.4); 0.5
Weak cough	34 (7.8)	8 (11.1)	3.3 (−3.6–13.2); 0.5

NIF – Negative inspiratory force; CI – Confidence interval

Supplementary Table 7: Multicollinearity diagnostics of continuous variables in the logistic regression model

Variables	Age	MV days	RR	pH
Age	1			
MV days	−0.1688	1		
RR	−0.0650	0.1940	1	
pH	−0.1149	0.3025	0.0625	1

Spearman's correlation rho between continuous predictors. No correlation coefficients > |0.7|. MV – Mechanical ventilation; RR – Respiratory rate; pH – Potential of hydrogen

Supplementary Table 8: Box-Tidwell test of linearity

Variables	MLE of lambda	Score statistic (*Z*)	*P*
Age	−0.080803	−0.2849	0.7757
MV days	0.472775	−1.3533	0.1760
RR	0.517750	−0.4095	0.6822
pH	20.421160	−0.8421	0.3997

Linearity between continuous predictors and the Logit (Log odds) of the outcome is an assumption of logistic regression. The assumption is satisfied if Box-Tidwell test's *P* value is >0.05. MV – Mechanical ventilation; RR – Respiratory rate; pH – Potential of hydrogen

Supplementary Table 9: Variance inflation factors of predictors in the model

Variables	VIF	1/VIF
Days of MV	1.09	0.921575
Age	1.04	0.958299
RR	1.04	0.964115
pH	1.04	0.965314
Mean VIF	1.05	

VIF <4 indicates that predictors are not correlated, and the absence of multicollinearity in the model. MV – Mechanical ventilation; RR – Respiratory rate; pH – Potential of hydrogen; VIF – Variance inflation factor