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ORIGINAL

Extubation in neurocritical care patients: the ENIO international prospective study

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Abstract

Purpose: Neurocritical care patients receive prolonged invasive mechanical ventilation (IMV), but there is poor specific information in this high-risk population about the liberation strategies of invasive mechanical ventilation.

Methods: ENIO (NCT03400904) is an international, prospective observational study, in 73 intensive care units (ICUs) in 18 countries from 2018 to 2020. Neurocritical care patients with a Glasgow Coma Score (GCS) ≤ 12, receiving IMV ≥ 24 h, undergoing extubation attempt or tracheostomy were included. The primary endpoint was extubation failure by day 5. An extubation success prediction score was created, with 2/3 of patients randomly allocated to the training cohort and 1/3 to the validation cohort. Secondary endpoints were the duration of IMV and in-ICU mortality.

Results: 1512 patients were included. Among the 1193 (78.9%) patients who underwent an extubation attempt, 231 (19.4%) failures were recorded. The score for successful extubation prediction retained 20 variables as independent predictors. The area under the curve (AUC) in the training cohort was 0.79 95% confidence interval (CI_{95}) [0.71–0.87] and 0.71 CI_{95} [0.61–0.81] in the validation cohort. Patients with extubation failure displayed a longer IMV duration (14 [7–21] vs 6 [3–11] days) and a higher in-ICU mortality rate (8.7% vs 2.4%). Three hundred and nineteen (21.1%)

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patients underwent tracheostomy without extubation attempt. Patients with direct tracheostomy displayed a longer duration of IMV and higher in-ICU mortality than patients with an extubation attempt (success and failure).

Conclusions: In neurocritical care patients, extubation failure is high and is associated with unfavourable outcomes. A score could predict extubation success in multiple settings. However, it will be mandatory to validate our findings in another prospective independent cohort.

Keywords: Extubation, Tracheostomy, Brain injury, Traumatic brain injury, Intra-cranial haemorrhage

Introduction

Invasive mechanical ventilation (IMV) is a key intervention in critical care patients [1]. Timely weaning from invasive ventilation may reduce the risk of hospital-acquired pneumonia [2], chronic illness related to intensive care unit (ICU) stay [3], and costs of care [1]. Neurocritical care patients undergo longer duration of IMV [4] and higher extubation failure rates [5] compared to the general population of critically ill patients. The liberation of IMV is thus of major interest in this population. The latest guidelines in neurocritical care patients highlight the poor level of evidence for extubation management or use of tracheostomy [6]. Neurocritical patients are usually poorly represented in randomized-controlled trials [7] and in cohort studies [7, 8]. It is uncertain which factors contribute to extubation success, and it is also unclear which patients may benefit from direct tracheostomy, i.e., tracheostomy without an initial extubation attempt [9]. All have attempted to provide scores predicting extubation success [10–13], but suffer from methodological issues (monocentric studies, lack of validation cohort). Consequently, evidence-based clinical guidance for extubation and tracheostomy in neurocritical care patients is lacking.

The primary objective of the international, prospective, multicentre ENIO cohort (Extubation strategies and in neuro-intensive care unit patients and associations with outcomes, NCT03400904) was to validate a score predictive of extubation success. Secondary objectives were to describe the causes of extubation failure, and describe the association between liberation strategies (extubation attempt, extubation failure, tracheostomy when extubation strategy was not applied) and outcomes.

Methods

The ENIO study is an investigator-initiated prospective, multicentre, international, observational study examining a cohort of neurocritical care patients requiring IMV (NCT03400904). The protocol has been previously published, and the plan for the primary analysis was finalized before cleaning and closing of the database [14]. The study protocol was approved by local institutional review boards according to local regulations. Initial approval was obtained from Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7-11-2017). Given the observational nature of the study, patient's consent was generally waived. In centres, where it was not waived, informed consent was obtained from patients' relatives, and afterwards from patients who recovered sufficiently. Oral and written information were provided, to the next-of-kin or legal representative, and to the patient whenever recovery was deemed adequate. The study was conducted according to the principles of the Declaration of Helsinki [15].

Take-home message

Neurocritical care patients display an extubation failure rate of 19% and direct tracheostomy is used as the primary liberation strategy of invasive mechanical ventilation in 21% of patients. Our validated score of extubation success prediction can be used in various settings worldwide.

Participating centres and subjects

We recruited centres through the national and international intensive care and neurocritical care networks, and site investigators (mailing lists and websites of the PROtective VENTilation network, the European Society of Intensive Care Medicine, the Colegio Mexicano de Medicina Critica, the Atlanréa group and the Société Française d'Anesthésie-Réanimation–SFAR research network). Participating centres screened and included consecutive patients during a period of at least 6 months. Medical and research personnel prospectively screened patients for inclusion. Neurocritical care patients (defined as patients with traumatic brain injury (TBI), subarachnoid aneurysmal haemorrhage (SAH), intracranial haemorrhage (ICH), ischemic stroke, central nervous system infection (brain abscess, empyema, meningitis, encephalitis or brain tumour) were eligible to this study, if they were ≥ 18 years, admitted to the ICU with a baseline Glasgow Coma Score (GCS) ≤ 12 before endotracheal intubation, required invasive mechanical ventilation ≥ 24 h and underwent an attempt to liberate the patient from the ventilator, defined as an extubation trial

and/or tracheostomy. Patients were excluded if < 18 years, pregnant, spinal cord injury above T4, resuscitated post-cardiac arrest, Guillain–Barré syndrome, motor neuron disease, muscular dystrophy and myasthenia gravis, death before extubation, withdrawal of life-sustaining treatment (WLST) in the first 24 h after ICU admission, end-of-life extubation, major respiratory co-morbidities (defined as chronic oxygen at home, chronic obstructive pulmonary disease grade III or IV of the Gold classification), and major chest trauma (Abbreviated Injury Score (AIS) ≥ 3). Patients who underwent tracheostomy prior to ICU admission were also excluded. Patients who died without any IMV liberation attempt were not eligible.

Data collection

Data were collected from the 26 of June 2018 to 15 of November 2020. Demographic and baseline data were collected [14]: age, height, weight, type and location (infra-tentorial) of brain injury, baseline GCS, neurocritical care management (barbiturate coma, therapeutic hypothermia, external ventricular drainage, decompressive craniectomy) and location of cerebral injury (posterior fossa). Respiratory data (e.g., mechanical ventilation parameters and laboratory results), sedation management, and the use of neuro-muscular blockade were collected at day 1, day 3 and day 7 after ICU admission. General in-ICU events such as health care-related pneumonia, trachea–bronchitis, acute respiratory distress syndrome and the occurrence of WLST were recorded.

The date of successful spontaneous breathing trial (SBT), first extubation attempt or tracheostomy was recorded. On the day of extubation, data on general management, such as the use of corticosteroids (post-extubation stridor prevention) or enteral nutrition discontinuation, were collected. A standardized clinical examination was performed on the day of extubation: vital signs (body temperature, heart rate, systolic arterial pressure), respiratory (including type and timing of SBT), physical examination (cough assessment, visual pursuit, eye-verbal-motor items of the GCS, gag reflex). The definition of these features was standardized according to previously described data (Online Resource, Text 1). For instance, cough strength was assessed using a 4-grade scale [16]: vigorous, moderate, weak, none. However, some quantitative indices such as the peak flow were not recorded. The exhaustive list of items collected the day of extubation is available on the Online resource. The timing and cause of re-intubation were recorded. Given the lack of consensus in the literature about the weaning and extubation of neurocritical patients [6], extubation strategies and post-extubation strategies (non-invasive mechanical ventilation) were performed according to each centre's own protocol.

Objectives

The primary objective was to validate a score predictive of extubation success [14], and the primary endpoint was extubation failure [14]. Extubation failure was defined as the necessity to re-intubate patients, after the first planned or accidental extubation attempt [17]. We have screened for any re-intubation, from extubation attempt, until ICU discharge. In case the ICU length-of-stay was longer than 28 days, we stopped the screening of re-intubation.

Since there is no consensus about the time-frame that defines extubation failure in neurocritical care patients [6, 7, 18, 19], we selected a time frame that captured more than 90% of extubation failure [20], to propose a pragmatic approach. In our study, the time-frame for reintubation was set at day 5. However, given the various thresholds proposed in the literature to define extubation failure (2 days [7, 17], within 5 days [7, 18, 19]), and as planned, we provided data regarding the 5-day extubation failure in the results, and 2-day extubation failure in the Online resource [14].

The secondary objectives were to describe the timing and causes of extubation failure, describe the practices in the management of IMV at day 1, day 3 and day 7 after admission, describe sedation practices at day 1, day 3 and day 7 after admission, and compare the characteristics of patients with direct tracheostomy vs patients with extubation attempt. Finally, we explored the association between the IMV liberation strategies (extubation success vs extubation failure, direct tracheostomy without extubation attempt vs extubation trial), and clinical outcomes (duration of invasive and non-invasive mechanical ventilation (mask and high-flow nasal oxygen cannula), ICU length of stay (LOS), in-ICU mortality and in-hospital mortality).

Statistical analysis

The analysis and reporting of the study comply with the TRIPOD statement (EQUATOR network: https://www.equator-network.org/reporting-guidelines/tripod-statement/). As detailed in published study protocol [14], we aimed to include at least 1500 patients in our cohort to screen 300 patients with an extubation failure. Data were expressed as means (SD), medians (interquartile range) and proportions as *N* (%). The characteristics and the outcomes of the patients in the extubation success group, the extubation failure group and the direct tracheostomy group were compared. Student's *t* test or Mann–Whitney *U* tests were used to compare continuous variables and chi-square tests were used for categorical variables.

To create a predictive score for extubation success, we excluded direct tracheostomy without extubation attempt, because these patients cannot be classified as extubation failure or success, withdrawal of life sustaining therapies during the ICU course which is a competing event with extubation failure. Patients who died without a context of withdrawal of life sustaining therapies and transferred to another facility were kept in the creation of the score, since reintubation was available. This data set was randomly split into a training set (2/3) and a validation set (1/3). The categorization of continuous variables was data-driven and assessment of plots of locally weighted regressions of the logit of extubation failure on each variable in the training set. Multiple imputation by chained equations (MICE) was performed in the setting of missing data [14]. Data were imputed five times via predictive mean matching. Swallowing attempts was the variable with the greatest proportion of missingness (8.3% overall).

Using this imputed data, we trained a logistic regression model with a group LASSO (Least Absolute Shrinkage Selection Operator) penalty [21]. The variables that the model were selected from was based upon literature review; the LASSO then retained variables with a nonzero coefficient. Collinearity is handled by the LASSO procedure, i.e., if 2 variables are highly correlated, only one will be retained in the final model [22, 23].

We used tenfold cross-validation to select the optimal λ based on the highest area under receiver operating characteristic curve (AUROC). To build a score that would be easier to calculate by hand at the bedside, we also built a simplified version by selecting the lowest λ for which the model retained a maximum of 12 coefficients. Each level of each variable was allocated points according to model coefficients. To create the score and convert the logit coefficients to points we took the following steps. First, we assigned all reference levels to have a coefficient of 0. Second, we identified the minimum and maximum value among coefficients for each variable (including reference level). Then, for each variable we calculated the difference between the minimum and maximum, and summed the differences to create a total weight. We took the difference between each coefficient and the minimum for that variable to create a raw point value. Finally, we multiplied the raw point value times 100 and divide by the total weight.

Model performance was estimated in both training and validation sets using only patients with complete data. Discrimination was evaluated with receiver operating characteristic (ROC) curves and AUCs. Calibration was evaluated with calibration plots and the Hosmer–Lemeshow test; the overall performance of the models was evaluated with the R2/Brier test. For the both models (complete and simplified), we then assessed sensitivity, specificity, and positive and negative predictive values for multiple thresholds chosen to maximize specificity. Positive and negative interval likelihood ratios were calculated for ranges of scores identified from the ROC curve and the distribution of scores in our data. The robustness of the model was tested by re-running the LASSO with 10 different seeds, and compared the list of variables selected by the LASSO.

Results

Patients and site characteristics

The first patient was enrolled in the Netherlands, in June 2018 and the last patient was included in France in October 2020. The flowchart of the study is available in Fig. 1. Of the final cohort ($N=1512$), patients suffered from TBI (725 (47.9%)), ICH (521 (34.5%)), SAH (269 (17.8%)), with a median age of 54 [36–66] years and a baseline GCS of 7 [5–9]. The patients' baseline characteristics are available in Table 1.

Primary objective

Extubation failure rate

In the entire ENIO cohort, 1193 (78.9%) patients had at least one extubation attempt, and 253 (21.2%) required reintubation within 28 days after the extubation attempt. National extubation failure rates varied from 0% up to 28.6% (Table 1). In our cohort, among 253 patients with extubation failure 231 (19.3%) patients required reintubation by day 5, which set the time-frame of extubation failure.

Patients in the 5-day extubation failure group had fewer TBI (82 (35.5%) vs 498 (51.8%), $p<0.001$), were older (59 [45–68] years vs 54 [34–65], $p=0.002$), and lower baseline GCS score (7 [5–8] vs 7 [5–9], $p=0.006$ (Table 1). Results for the baseline characteristics of the day 2 extubation failure group are available in the Online resource, Table 1.

Extubation success factors: univariate analysis

There were no significant differences in general clinical management on the day of extubation between the two groups (day 5 extubation failure). The vital signs on the day of extubation significantly associated with success included higher body temperature, higher heart rate and lower SpO_2. The airway clinical features associated with success were swallowing attempts, the presence of a gag reflex, and the frequency of endo-tracheal suctioning. The arousal and neurologic features associated with extubation success were visual pursuit, the total GCS and the motor score of the GCS (Table 2). Patients in the day 2 extubation failure group did not display significant differences with the success group (Online resource, Table 2) [17].

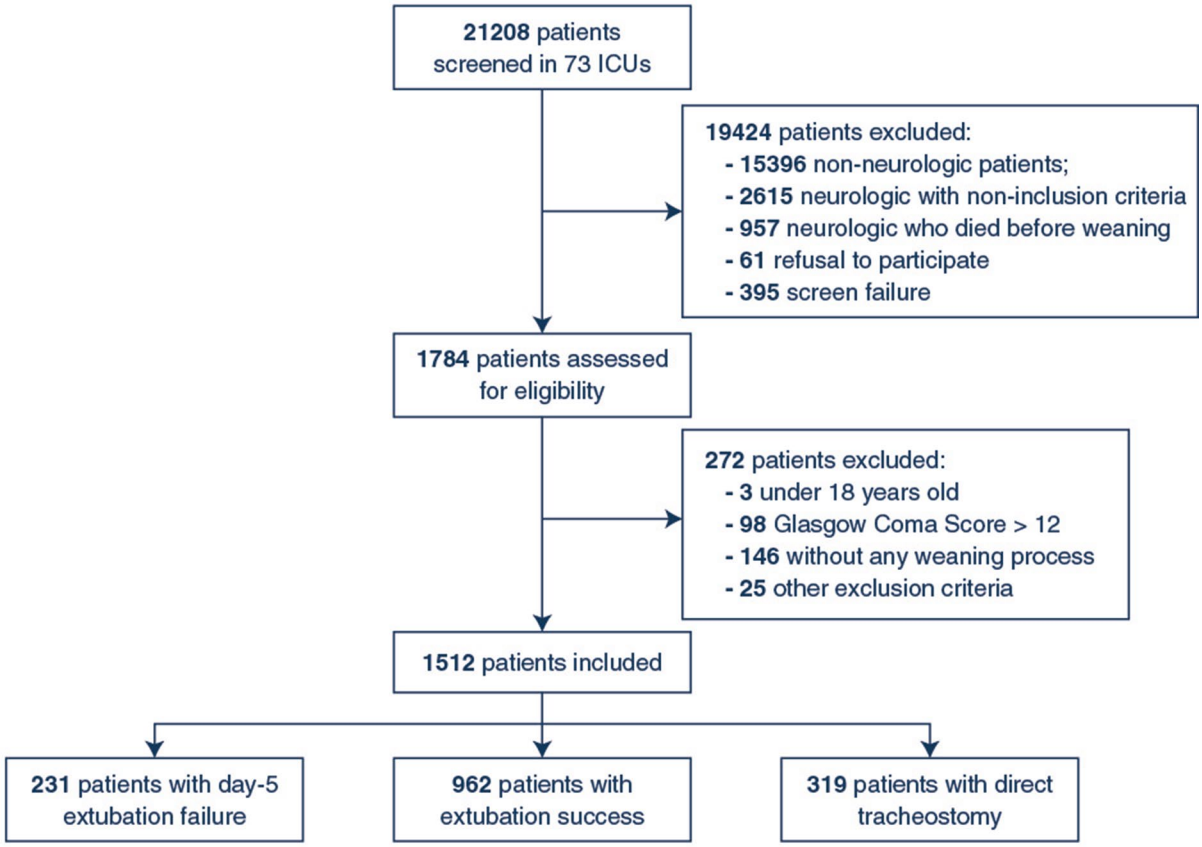

Fig. 1 Flowchart of the study

Successful extubation prediction score

Of the cohort, 1106 patients were eligible to build the score to predict extubation success, resulting in 737 individuals in the training set and 369 in the validation set. The LASSO model with the optimal λ retained 20 variables (Online resource, Table 3). The AUC in the training cohort ($N=308$) was 0.79 95% confidence interval (CI_{95}) [0.71–0.87] and 0.71 CI_{95} [0.61–0.81] in the validation cohort ($N=166$). The ROC curve, the calibration plot and the decision curve of the complete score in the validation cohort are available in Fig. 2. The ROC curve, the calibration plot and the decision curve of the complete score in the validation cohort are available in the Online Resource, Fig. R1.

Given the number of variables retained in the optimal model, a simplified user-friendly score was also validated. Only 7 predictors were kept in the simplified score (Online resource, Table 4): TBI, vigorous cough, gag reflex, swallowing attempts, endotracheal suctioning ≤ 2 times per hour, GCS motor score $=6$ and body temperature the day of extubation. The AUC of the score was 0.79 CI_{95} [0.71–0.86] in the training cohort and 0.65 CI_{95} [0.53–0.76] in the validation cohort. The ROC Curve, the calibration plot and the decision curves of the simplified score are available in the Online resource, Fig. 1.

The sensitivity, specificity, positive and negative predictive values of the complete score are available in Table 3 and the values of the simplified score are available in the Online resource, Table 4. Interval likelihood ratios for both scores are in the Online resource, Tables 6 and 7. The likelihood ratio of extubation success for a complete score ≥ 70 points (theoretical range 0–91) was 3.67.

In the analysis testing the robustness of our score (10 randomly generated seeds), the AUC in the test set ranged from 0.646 to 0.848, and the Brier score ranged from 0.089 to 0.119. This supplementary analysis is available in the Online resource, Text 2.

Secondary objectives

Causes of extubation failure

In the day 5 failure group, the primary causes of extubation failure were neurologic failure (92 (39.8%) patients), respiratory failure (126 (54.5%) patients) and airway failure (87 (37.7%) patients). Data regarding the causes

Table 1 Baseline characteristics of patients with extubation trial and day 5 extubation failure

	Day 5 extubation failure *N* = 231	Extubation success *N* = 962	OR CI_{95}	*p* value	Overall cohort *N* = 1512	Missing data *N* (%)
Country			5.8 [0.2–161.9]	0.2		–
Argentina	6 (2.6%)	35 (3.6%)			45 (3%)	
Bangladesh	1 (0.4%)	1 (0.1%)			2 (0.1%)	
Belgium	3 (1.3%)	17 (1.8%)			20 (1.3%)	
Canada	4 (1.7%)	8 (0.8%)			14 (0.9%)	
Egypt	0	1 (0.1%)			1 (0.1%)	
France	127 (55%)	506 (52.6%)			669 (44.2%)	
Greece	4 (1.7%)	10 (1%)			33 (2.2%)	
India	0	21 (2.2%)			80 (5.3%)	
Italy	21 (9.1%)	36 (3.7%)			131 (8.7%)	
Japan	3 (1.3%)	16 (1.7%)			31 (2.1%)	
Libya	1 (0.4%)	7 (0.7%)			11 (0.7%)	
Mexico	19 (8.2%)	131 (13.6%)			203 (13.4%)	
Netherlands	9 (3.9%)	36 (3.7%)			53 (3.5%)	
Qatar	1 (0.4%)	10 (1%)			21 (1.4%)	
Spain	1 (0.4%)	17 (1.8%)			27 (1.8%)	
Switzerland	15 (6.5%)	49 (5.1%)			79 (5.2%)	
United Kingdom	10 (4.3%)	34 (3.5%)			50 (3.3%)	
USA	0	6 (0.6%)			9 (0.6%)	
Uruguay	6 (2.6%)	21 (2.2%)			33 (2.2%)	
Cause of admission						
TBI	82 (35.5%)	498 (51.8%)	0.5 [0.4–0.7]	< 0.001	725 (47.9%)	1 (0.1%)
ICH	92 (39.8%)	301 (31.3%)	1.5 [1.1–1.9]	0.01	521 (34.5%)	1 (0.1%)
SAH	47 (20.3%)	162 (16.8%)	1.3 [0.9–1.8]	0.2	269 (17.8%)	4 (0.3%)
Ischemic Stroke	25 (10.8%)	83 (8.6%)	1.3 [0.8–2]	0.3	141 (9.3%)	4 (0.3%)
CNS infection	10 (4.3%)	41 (4.3%)	1 [0.4–2]	0.9	74 (4.9%)	4 (0.3%)
Brain tumor	10 (4.3%)	54 (5.6%)	0.8 [0.4–1.5]	0.4	72 (4.8%)	6 (0.4%)
General characteristics						
Age (years)	59 [45–68]	54 [34–65]	1.01 [1–1.02]	0.003	54 [36–66]	12 (0.8%)
Height (cm)	173 [165–179]	170 [165–177]	1 [0.9–.02]	0.4	170 [165–176]	46 (3%)
Weight (kg)	76 [66–90]	75 [65–85]	1 [0.9–1.01]	0.1	75 [65–85]	10 (0.7%)
BMI (kg m^{-2})	26 [23–29]	25 [23–29]	1 [0.9–1.04]	0.1	26 [23–29]	46 (3%)
Gender						
Male	161 (69.7%)	646 (67.2%)	1.1 [0.8–1.5]	0.5	998 (66%)	–
Female	70 (30.3%)	316 (32.8%)			514 (34%)	
COPD I–II	14 (6.1%)	31 (3.2%)	1.9 [1–3.6]	0.05	51 (3.4%)	1 (0.1%)
NYHA ≥ 2	6 (2.6%)	32 (3.3%)	0.8 [0.3–1.7]	0.6	44 (2.9%)	1 (0.1%)
Hypertension	86 (37.2%)	271 (28.2%)	1.5 [1.1–2]	0.007	451 (29.8%)	1 (0.1%)
Active smoking	50 (21.6%)	209 (21.7%)	1 [0.7–1.4]	0.9	330 (21.8%)	9 (0.6%)
Diabetes mellitus	29 (12.6%)	112 (11.6%)	1.1 [0.7–1.7]	0.7	183 (12.1%)	1 (0.1%)
History of malignancy	11 (4.8%)	44 (4.6%)	1 [0.5–2]	0.9	68 (4.5%)	1 (0.1%)
Neurologic characteristics						
GCS total	7 [5–8]	7 [5–9]	0.9 [0.9–1]	0.006	7 [5–9]	
GCS Eye	1 [1, 2]	1 [1, 2]	0.8 [0.7–1]	0.03	1 [1, 2]	45 (3%)
GCS Verbal	1 [1, 2]	1 [1, 2]	0.8 [0.7–0.9]	0.01	1 [1, 2]	53 (3.5%)
GCS Motor	4 [2–5]	4 [3–5]	0.9 [0.8–0.9]	0.04	4 [2–5]	45 (3%)
Anisocoria	0 [0–1]	0 [0–1]	1.1 [0.8–1.5]	0.7	412 (27.2%)	4 (0.3%)
ICP monitoring	100 (43.3%)	447 (46.5%)	0.9 [0.7–1.2]	0.4	642 (42.5%)	2 (0.1%)
EVD	86 (37.2%)	263 (27.3%)	1.6 [1.2–2.1]	0.003	442 (29.2%)	1 (0.1%)

Table 1 (continued)

	Day 5 extubation failure *N* = 231	Extubation success *N* = 962	OR CI_{95}	*p* value	Overall cohort *N* = 1512	Missing data *N* (%)
Posterior fossa injury	18 (7.8%)	51 (5.3%)	1.5 [0.8–2.6]	0.2	87 (5.8%)	2 (0.1%)
Therapeutic hypothermia	7 (3%)	42 (4.4%)	0.7 [0.3–1.4]	0.6	61 (4%)	1 (0.1%)
Barbiturate coma	9 (3.9%)	53 (5.5%)	0.7 [0.3–1.4]	0.3	86 (5.7%)	1 (0.1%)
Intra-cranial neurosurgery	84 (36.4%)	377 (39.2%)	0.9 [0.7–1.2]	0.4	609 (40.3%)	2 (0.1%)
Decompressive craniectomy	41 (17.7%)	156 (16.2%)	1.1 [0.8–1.6]	0.6	291 (19.2%)	1 (0.1%)

TBI traumatic brain injury, *ICH* intra-cranial hemorrhage, *SAH* subarachnoid hemorrhage, *CNS* central nervous system, *COPD* chronic obstructive pulmonary disease, *ICP* intra-cranial pressure, *EVD* external ventricular drainage, *GCS* Glasgow Coma Score, *NYHA* New-York Heart Association

of day 5 and day 2 extubation failure is available in the Online resource, Table 8.

Ventilator settings and sedation practices

Description of ventilatory settings, respiratory parameters, biology and sedation practices on day 1, day 3 and day 7 after ICU admission is available in the Online resource, Table 9.

Direct tracheostomy

Direct tracheostomy was performed in 319 (21.1%) patients, the median timing of tracheostomy was 9 [5–15] days after starting IMV. The main reasons for tracheostomy were severe neurologic impairment (237 (74.3%) patients), airway impairment (51 (16%) patients) and severe face/neck trauma (14 (4.4%) patients). We observed major differences in the use of tracheostomy between countries ($p < 0.001$) (Online resource, Table 10).

Extubation failure, tracheostomy and outcomes

Patients with day 5 extubation failure suffered from more frequent hospital-acquired pneumonia, Acute Respiratory Distress Syndrome, a longer duration of IMV and a higher in-ICU mortality rate (Online resource, Table 11). The analysis with day 2 extubation failure displayed similar results (Online resource, Table 12). Patients with direct tracheostomy experienced more hospital-acquired pneumonia, a longer duration of IMV and a higher in-ICU mortality rate, compared to patients without direct tracheostomy (Online resource, Table 13).

Discussion

In the international, prospective ENIO cohort, we found a wide variation in practices of extubation management and tracheostomy between geographic areas in neurocritical care patients. We also found that: (1) the extubation failure rate is around 20%; (2) a score can predict extubation success; (3) both patients with tracheostomy and extubation failure displayed prolonged duration of IMV, higher rates of respiratory infections, and higher rate of mortality.

Neurocritical patients present specific challenges regarding extubation due to the nature of their injuries (altered levels of consciousness complicate safe extubation and aspiration prevention) [24]. The WIND classification [25] may not be applicable to neurocritical care patients, as patients may easily pass SBT, but extubation can be delayed because of neurologic and airway impairment [16]. The poor level of evidence in the neurocritical care literature explains the major variability we observed between countries regarding the management of extubation and tracheostomy.

Extubation failure remains common in the general population of critically ill patients (10–15%) [5, 7] and is as high as 25% in patients with neurologic illness [5]. In previous cohorts with neurologic patients [11–13], the extubation failure rate was around 21–25%. The definition of extubation failure varies substantially between studies [12]. In addition, there is currently no consensus on the timeframe to define extubation failure. It was recently proposed to extend the timeframe for extubation failure from 3 days [18] to 7 days after extubation [19]. Miltiades et al. [20] proposed to use a timeframe that captures > 90% of extubation failures. Based on this pragmatic approach, a 5-day time frame was selected to account for > 90% of failures and perform the primary analysis. In addition, we decided to separate patients with direct tracheostomy from patients with extubation attempt, since these patients will not meet the primary outcome. Patients with a late tracheostomy after an extubation attempt, were kept in the analysis. We thus chose a clear definition of extubation failure by discarding tracheostomy or non-invasive ventilation [12].

More than 20 years ago, Coplin et al. [16] pointed out that delaying extubation in the context of successful SBT for safety reasons (neurological recovery) was associated with increased IMV duration and health-acquired pneumonia. Recently, few cohorts have developed specific scores to predict successful extubation in neuro-critical patients [11–13]. These scores include general features (age [11, 13], fluid balance [13]), level of consciousness

Table 2 Management and clinical features the day of extubation

	Day 5 extubation failure *N* = 231	Extubation success *N* = 962	OR CI_{95}	*p* value	Missing data *N* (%)
General management the day of extubation					
Enteral nutrition discontinuation	137 (59.3%)	602 (62.6%)	0.8 [0.6–1.1]	0.2	28 (2.3%)
Cuff leak test performance	77 (33.3%)	371 (38.6%)	0.8 [0.6–1.1]	0.2	34 (2.9%)
Steroids for PES prevention	46 (19.9%)	206 (21.4%)	0.9 [0.6–1.3]	0.6	11 (0.9%)
SBT					
T piece breathing	77 (33.3%)	368 (38.3%)	0.8 [0.6–1.1]	0.2	32 (2.7%)
T piece duration (mn)	60 [30–120]	60 [30–120]	1 [1–1]	0.5	–
CPAP	61 (26.4%)	256 (26.6%)	1 [0.7–1.3]	0.9	45 (3.8%)
CPAP duration (mn)	120 [50–360]	120 [60–360]	1 [1–1]	0.5	–
Pressure Assist	100 (43.3%)	413 (42.9%)	1 [0.7–1.4]	0.9	87 (7.3%)
Pressure Assist duration (mn)	60 [30–120]	80 [30–240]	0.99 [0.99–0.99]	0.006	
Planned	211 (91.3%)	896 (93.1%)	0.6 [0.4–1.1]	0.09	12 (1%)
Temperature (°C)	37.3 [37–37.8]	37 [36.7–37.5]	1.7 [1.4–2]	< 0.001	30 (2.5%)
Tidal volume (mL)	458 [420–510]	480 [420–550]	0.99 [0.99–0.99]	0.04	97 (8.1%)
PEEP (cmH_2O)	5 [5–7]	5 [5, 6]	1.1 [1–1.3]	0.003	61 (5.1%)
SAP (mmHg)	140 [123–153]	137 [125–150]	1 [1–1]	0.3	30 (2.5%)
SpO_2 (%)	98 [96–99]	98 [97–100]	0.9 [0.8–0.9]	0.01	24 (2%)
Heart rate (/mn)	87 [72–99]	83 [70–95]	1 [1–1]	0.004	22 (1.8%)
SpO_2 at the end of SBT (%)	98 [95–99]	98 [96–99]	0.9 [0.9–1]	0.6	760 (63.7%)
RR at the end of SBT (/mn)	21 [17–25]	20 [17–23]	1 [1–1]	0.2	764 (64%)
SAP at the end of SBT (mmHg)	141 [130–156]	135 [123–153]	1 [1–1]	0.1	764 (64%)
Clinical features					
SBT–extubation delay (days)	1 [0–2]	0 [0–2]	1 [1–1]	0.4	112 (9.4%)
Visual pursuit	167 (72.3%)	751 (78.1%)	0.7 [0.5–0.9]	0.02	62 (5.2%)
Swallowing attempts	165 (71.4%)	746 (77.5%)	0.6 [0.4–0.9]	0.007	99 (8.3%)
Gag reflex			0.5 [0.3–0.9]	0.01	52 (4.4%)
Present	122 (52.8%)	570 (59.3%)			
Not done	79 (34.2%)	302 (31.4%)			
Endo-tracheal suctioning			2.1 [1.4–3.3]	< 0.001	34 (2.9%)
> 3 times/hour	101 (43.7%)	570 (59.3%)			
2–3 times/hour	28 (12.1%)	45 (4.7%)			
1–2 times/hour	50 (21.6%)	196 (20.4%)			
< 1 times/hour	101 (43.7%)	570 (59.3%)			
Cough			0.6 [0.1–1.8]	0.4	81 (6.8%)
Vigorous	71 (30.7%)	385 (40%)			
Moderate	102 (44.2%)	397 (41.3%)			
Weak	42 (18.2%)	93 (9.7%)			
None	3 (1.3%)	19 (2%)			
GCS total	11 [9–13]	11 [10–14]	0.9 [0.8–0.9]	< 0.001	
GCS Eye	4 [3, 4]	4 [3, 4]	0.9 [0.7–1.1]	0.2	34 (2.9%)
GCS Verbal	1 [1–4]	1 [1–4]	0.8 [0.7–0.9]	< 0.001	59 (4.9%)
GCS Motor	6 [5, 6]	6 [5, 6]	0.9 [0.7–1]	0.1	33 (2.8%)
Physiotherapy	173 (74.9%)	708 (73.6%)	1.1 [0.8–1.6]	0.5	34 (2.9%)
Prophylactic physiotherapy	119 (51.5%)	591 (61.4%)	0.4 [0.3–0.6]	< 0.001	317 (26.6%)

Regarding the different strategies of SBT (T-tube, CPAP, pressure assist mode), we provide the duration of SBT (minutes) performed in the 6 h before extubation attempt. We did not record the number of SBTs performed in the days preceding extubation attempt

PES post-extubation stridor, *CPAP* continuous positive airway pressure, *RR* respiratory rate, *SAP* systolic arterial pressure, *SBT* spontaneous breathing trial, *GCS* Glasgow Coma Score

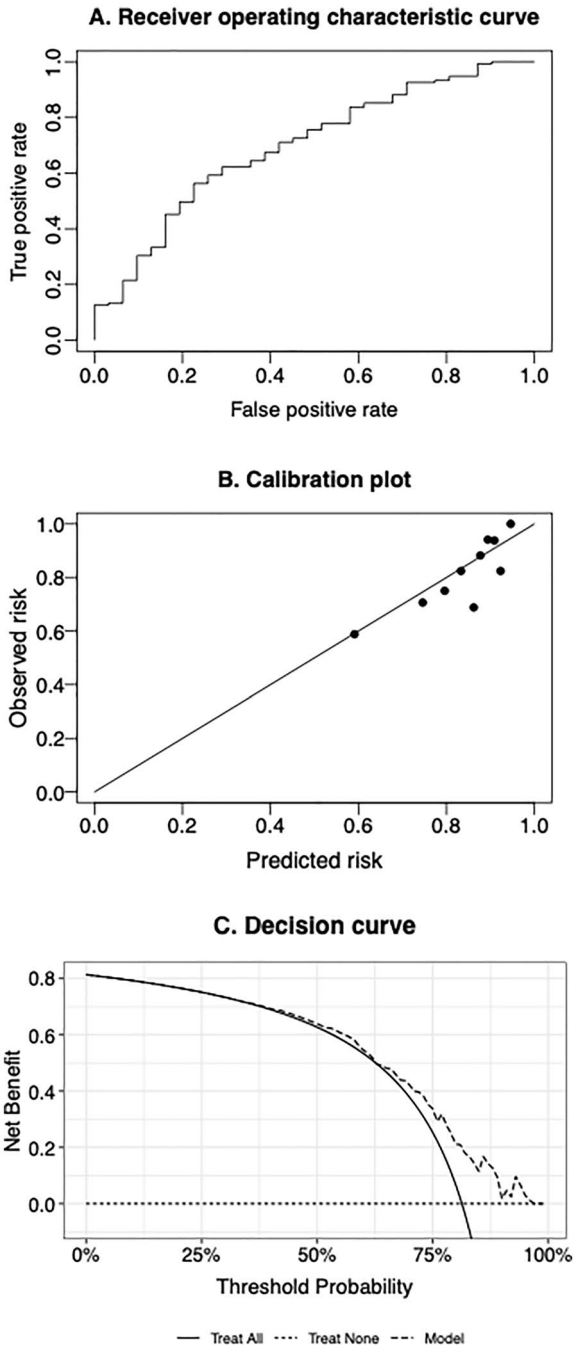

Fig. 2 ROC curve, calibration plot and decision curve and the complete score. The AUC of the ROC curve of the complete score was 0·71 CI_{95} [0·61–0·81] in the validation cohort. Hosmer–Lemeshow test in the validation set: $p = 0{\cdot}41$. The Brier test of the global score was 0·08 in the training cohort and 0·14 in the validation cohort

(GCS [11], Coma-Recovery-Scale [12], specific features, such as visual pursuit [11, 12]) and airway evaluation (swallowing attempts [11]) to predict extubation success. However, most cohorts are monocentric, do not provide

Table 3 Sensitivity, specificity, positive and negative values of the different thresholds of the complete score

Thresholds	Sensitivity	Specificity	Positive Predictive Pressure	Negative Predictive Pressure
100	0	1	NaN	0.19
90	0.007	1	1	0.19
88	0.01	1	1	0.19
82	0.02	1	1	0.19
80	0.04	1	1	0.19
78	0.06	1	1	0.19
77	0.08	1	1	0.2
76	0.11	1	1	0.21
75	0.13	1	1	0.21
74	0.14	0.97	0.95	0.21
73	0.16	0.97	0.95	0.21
72	0.18	0.94	0.92	0.21
71	0.21	0.94	0.94	0.21
70	0.24	0.94	0.94	0.22
69	0.28	0.94	0.95	0.23
68	0.33	0.90	0.94	0.24
67	0.39	0.90	0.95	0.25
66	0.43	0.84	0.92	0.25
65	0.47	0.81	0.91	0.26
64	0.51	0.81	0.92	0.27
63	0.54	0.81	0.92	0.29
62	0.58	0.81	0.93	0.30
61	0.61	0.77	0.92	0.31
60	0.644	0.68	0.90	0.30
59	0.67	0.55	0.87	0.29
58	0.73	0.48	0.86	0.29
57	0.73	0.45	0.85	0.27
56	0.75	0.45	0.86	0.29
54	0.79	0.45	0.86	0.33
53	0.81	0.42	0.86	0.33
52	0.84	0.39	0.86	0.35
51	0.86	0.32	0.85	0.34
50	0.87	0.32	0.85	0.37
49	0.90	0.32	0.85	0.42
48	0.90	0.32	0.85	0.43
47	0.92	0.26	0.84	0.42
46	0.93	0.23	0.84	0.44
45	0.93	0.16	0.83	0.36
44	0.94	0.16	0.83	0.38
43	0.95	0.16	0.83	0.42
41	0.96	0.16	0.83	0.45
39	0.97	0.16	0.83	0.56
38	0.98	0.16	0.84	0.62
37	0.99	0.16	0.84	0.71
36	0.99	0.13	0.83	0.67
35	0.99	0.1	0.83	0.6
34	0.99	0.06	0.82	0.5

Table 3 (continued)

Thresholds	Sensitivity	Specificity	Positive Predictive Pressure	Negative Predictive Pressure
33	1	0.06	0.82	1
25	1	0.03	0.82	1
21	1	0	0.81	NaN

extensive neurologic and airway exploration at extubation (e.g., gag reflex [16]), and most of all lack external validation that could ensure generalizability of the scores [11–13]. To the best of our knowledge, ENIO is the first to propose a score developed on a large sample of international data and easily calculated at the bedside. The items identified as predictors of extubation success were also consistent with those identified in previous studies [11, 12, 16]. However, a threshold of 75 of the complete score with a perfect Positive Prediction Value (100%) could encourage systematic extubation, but bears low sensitivity and will be rarely seen in patients. On the contrary a threshold of 33 with a perfect Negative Predictive Value bears low specificity. The choice of the adequate balance between Positive and Negative Prediction value remains open to discussion. Future prospective trials are necessary to demonstrate whether our score could help physicians in a proactive extubation strategy to decrease morbidity associated with both delayed extubation and/or extubation failure [16].

Direct tracheostomy is a potential strategy to secure the liberation of IMV. There is conflicting evidence that tracheostomy timing could alter the short- and long-term outcomes of patients in the general ICU population [26, 27]. In a meta-analysis focusing on neuro-critical patients, it was reported that early tracheostomy could decrease mortality and the duration of IMV compared to late tracheostomy [9]. In a randomized-controlled trial testing two timing of tracheostomy in patients with an expected prolonged duration of IMV [28], nearly half patients in the late tracheostomy group did not undergo the intervention. These results underline the inability of clinicians to accurately select patients that could benefit from tracheostomy. Further data are needed to guide decision-making for direct tracheostomy in neurocritical care patients.

Strengths and limitations

Our study has strengths. First, the cohort has a large sample size, and was elaborated in various settings. Second, we elaborated a pre-planned analysis that was followed. Finally, the clear endpoints and objectives should end generalizability of our results.

The present study has nonetheless several limitations. Our data can be used to identify associations between outcomes and liberation strategy, but because of the study design, we cannot make causal inferences. Data collection was limited to specific timepoints, such as the first day of successful SBT or the day of tracheostomy. We deliberately chose to focus on major clinical features the day of extubation and in-ICU outcomes, to ensure feasibility of data collection. Since this was an open study, we cannot rule out a Hawthorne effect on extubation practices, with a modification of patient's management. In addition, important ICU-specific factors such as nursing ratio, the presence of respiratory therapist, local protocols, post-extubation management such as high flow nasal cannula oxygen were not accounted for in this study. However, centres performed extubation according to local protocols. Their impact will be specifically studied in an ancillary study (Online resource, Text 3). Finally, the validation cohort is drawn from the same sample as the learning cohort. These two samples are not independent, and it will be mandatory to validate our findings in another prospective independent cohort.

Conclusions

In this international cohort of neurocritical care patients, extubation failure is high and should be monitored in the first 5 days after an extubation attempt. Neurocritical patients undergoing direct tracheostomy instead of extubation attempt, appear to be a selected group of patients with greater severity, and should be specifically explored.

Supplementary Information

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Declarations

Conflicts of interest

The authors do not have financial or non-financial interest, directly or indirectly related to this work.

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