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Associations of positive end-expiratory pressure (PEEP) with extubation failure and clinical outcomes in invasively ventilated patients with acute brain injury: A secondary analysis of the ENIO study

Denise Battaglini [a,b,*], Raphael Cinotti [c], Karim Asehnoune [c], Andrea Loggini [d,j], Luca Montagnani [b], Lorenzo Ball [a,b], Francesca Gualdi [a,b], Patricia R.M. Rocco [e], Marcus J. Schultz [f,g,h,i], Nicolò Antonino Patroniti [a,b], Chiara Robba [a,b], For the ENIO collaborators[1]

[a] Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Italy
[b] Anesthesia and Intensive Care, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
[c] Department of Anaesthesia and Critical Care, Centre Hospitalier Universitaire de Nantes, Nantes, France
[d] Brain and Spine Institute. Southern Illinois Healthcare, Carbondale, IL, United States
[e] Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[f] Department of Clinical Medicine, University of Oxford Nuffield, Oxford, UK
[g] Department of Intensive Care, Amsterdam University Medical Centers, Amsterdam, the Netherlands
[h] Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand
[i] Department of Anesthesia, General Intensive Care and Pain Management, Division of Cardiothoracic and Vascular Anesthesia & Critical Care Medicine, Medical University of Vienna, Vienna, Austria
[j] Southern Illinois University School of Medicine, Carbondale, IL, United States

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ABSTRACT

Background: Invasive mechanical ventilation (IMV) is crucial for managing acute brain injury (ABI) patients, yet the effects of positive end-expiratory pressure (PEEP) on outcomes are not well understood. This study aimed to evaluate the relationship between PEEP levels and risk of extubation failure as well as intensive care unit (ICU) mortality in ABI patients.

Methods: This post-hoc analysis of the ENIO study included 1512 ABI patients from the ENIO cohort, excluding those without available data on PEEP at day 1 and who never received an extubation trial. PEEP levels were recorded at days 1, 3, 7, and on the day of extubation. Logistic regression assessed the association between PEEP and extubation failure, while Cox proportional hazards regression analyzed ICU mortality.

Results: Among 1154 included patients, extubation failure occurred in 21.2 % and ICU mortality was 3.7 %. Higher median PEEP at days 1, 3, and 7 was independently associated with increased odds ratio (OR) of extubation failure (OR = 1.13; 95 %CI = 1.01–1.26; $p = 0.0294$). At the time of extubation, higher PEEP was also significantly associated with extubation failure (OR = 1.13; 95 %CI = 1.02–1.25; p = 0.0218) and ICU mortality (Hazard Ratio, HR = 1.38; 95 %CI = 1.12–1.69; p = 0.0026). However, at sensitivity analyses adjusted for acute respiratory distress syndrome (ARDS), PEEP was no longer significantly associated with outcomes, while ARDS itself was an independent predictor of extubation failure.

Conclusions: Extubating ABI patients at higher PEEP levels was associated with an increased risk of extubation failure and ICU mortality. However, this association likely reflects underlying respiratory pathology or disease severity. Our findings suggest that PEEP level may serve as a surrogate marker for extubation readiness, rather than a modifiable risk factor, and highlight the need for individualized assessment prior to extubation.

* Corresponding author at: Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy.
E-mail address: denise.battaglini@unige.it (D. Battaglini).

[1] **List of ENIO Collaborators:** to be listed in **PubMed.**

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1. Introduction

Patients with acute brain injury (ABI) may require invasive mechanical ventilation (IMV) to improve systemic and cerebral oxygenation and carefully control carbon dioxide levels [1]. However, these patients often require long periods of IMV due to depressed neurological status, which can impair airway patency, swallow ability, gag reflexes, and respiratory drive [2]. Conventional IMV for patients with ABI may conflict with lung protective ventilation strategies [3], potentially exacerbating pulmonary and systemic inflammation and increasing the risk of ventilator-induced lung injury (VILI) [4].

Among IMV parameters, positive end-expiratory pressure (PEEP) is considered one of the most critical variables for brain physiology. From a lung perspective, PEEP enhances oxygenation and promotes lung recruitment, while minimizing the harmful effects of the cyclical opening and closing of alveolar units [5]. However, PEEP can also reduce cardiac output and increase physiological dead space, leading to intracranial arterial vasodilatation and increased cerebral blood volume. Additionally, PEEP can raise intrathoracic and intra-abdominal pressure, which may impact intracranial pressure (ICP) and cerebral perfusion pressure (CPP) [6,7]. Historically, concerns regarding these pathophysiological effects led to the widespread use of zero PEEP strategy in ABI patients [8]. However, with a growing understanding of pulmonary and cerebral physiology, recent guidelines recommend PEEP levels like those used in the general ICU population [4,9]. Nonetheless, the PROLABI trial did not demonstrate any benefit in low vs higher PEEP in ABI patients [10], raising concerns about the safety of lung-protective strategies in this population. Given the unique physiological challenges of ABI patients, including altered cerebral perfusion and the risk of secondary brain injury, appropriate PEEP selection is essential [7].

This is a secondary analysis of the ENIO trial, aimed to describe the use of PEEP in ABI patients and assess its association with extubation failure and ICU mortality at multiple time points throughout their care. We hypothesized that in patients with ABI, higher PEEP during IMV is associated with an increased rate of extubation failure and higher ICU mortality compared to lower PEEP levels.

2. Methods

2.1. Study design and consent

This is a *post-hoc* analysis of the ENIO study (NCT03400904) [2], a prospective multi-center international observational cohort study, endorsed and promoted by the PROtective VEntilation Network, European Society of Intensive Care Medicine, Society of Critical Care Medicine, French Society of Anesthesiology and Critical Care (SFAR), and Colegio Mexicano de Medicina Critica. Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7/11/2017, provided the initial permission. The local ethics committees at each participating center granted permission to conduct the ENIO study. In accordance with local laws and regulations, both written and verbal informed consent was given to participate in the ENIO study. The Medical Research Involving Human Subjects Act (WMO) and the Declaration of Helsinki's tenets guided the ENIO investigation [11]. Data management, monitoring, and reporting of the study were performed in accordance with the ICH-GCP Guidelines [12]. The ENIO study and this *post-hoc* analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13], *Supplementary Material (SM) Item S1*.

2.2. Study endpoints and definitions

The primary endpoint was extubation failure, defined as the need for reintubation within 5 days after an extubation attempt. Secondary endpoints were ICU mortality and the description of PEEP trajectories and variability. Extubation failure was defined as the need for reintubation within 5 days after an extubation attempt, as defined in the ENIO study [2].

Visual pursuit is defined as the ability of the eyes to smoothly follow a moving object. ARDS was defined according to the Berlin definition [14].

At each time-points (Day 1, 3, 7, and the Day of Extubation), patients were dichotomized according to a PEEP level > 5 cmH_2O and ≤ 5 cmH_2O. Definition for low-PEEP ≤ 5 cmH_2O was previously adopted in patients without acute respiratory distress syndrome (ARDS) in the RELAx trial [15]. Considering that in the trial High-PEEP was defined as >8 cmH_2O, and that our median PEEP value at day 1,3,7 was 5.5 cmH_2O, we decided to binary classify patients using PEEP>5 cmH_2O and ≤ 5 cmH_2O [15].

2.3. Patients and data collection

The inclusion and exclusion criteria of the ENIO study have been previously published [2]. Eligible participants for the ENIO study were neurocritical care patients aged 18 or older, with a Glasgow Coma Score (GCS) of 12 or lower before intubation, requiring IMV for at least 24 h, and undergoing an extubation trial. Exclusion criteria included individuals under 18 or pregnant, those with spinal cord injuries above T4, resuscitated postcardiac arrest, certain neuromuscular conditions, or who died before extubation. Additionally, patients withdrawing life-sustaining treatment within 24 h, those with severe respiratory comorbidities or major chest trauma, and those with prior tracheostomy were also excluded. Patients who died without an attempt at ventilation liberation were not eligible. For this post-hoc study, we excluded patients without available data on PEEP at day 1 and those who were never extubated.

Demographic and baseline information [age, body mass index, (BMI), medical history] and origin injury data [traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), ischemic stroke (IS), central nervous system (CNS) infection, and brain tumor] were obtained from the ENIO dataset. Neuro-surgical management [decompressive craniectomy, ICP monitoring, external ventricular drainage (EVD), posterior fossa injury, use of therapeutic hypothermia, neurosurgery]; airway management data [tracheostomy placement, extubation success]; and severity of brain injury [GCS, episode of anisocoria, GCS motor score]; in-ICU events and outcomes [reintubation within 5 days from extubation, in-ICU and in-hospital mortality, length of stay in ICU, ventilator-associated pneumonia (VAP), ARDS].

Data on days 1, 3, and 7, and at extubation included: ventilatory setting and blood gas analysis [ventilator mode (pressure assist, pressure control, volume assist, pressure support), respiratory rate (breaths/min), PEEP (cmH_2O), tidal volume (mL and mL/kg of predicted body weight [PBW]), arterial partial pressure of oxygen (PaO_2, mmHg) to fraction of inspired oxygen (FiO_2), arterial pH (pHa), arterial partial pressure of carbon dioxide ($PaCO_2$, mmHg), Driving pressure (calculated as Pplat - PEEP, cmH_2O) [16]], sedation strategy [midazolam, propofol, dexmedetomidine, pentothal], and use of neuromuscular blockers. All data were collected around 8:00 AM.

2.4. Statistical analyses

Continuous variables are presented as mean $\pm$ standard deviation (SD) or medians and interquartile ranges [IQR], while categorical variables are expressed as numbers with percentages (%). Independent *t*-tests or Mann-Whitney *U* tests were conducted for continuous variables, and Chi-square tests were used for categorical variables, as appropriate. The assumptions of normality and homogeneity of variances were

assessed prior to performing *t*-tests.

Logistic regression analyses were performed to assess the association between PEEP levels and the likelihood of extubation failure. The forced entry strategy for regression analysis was adopted, with predictors selected based on clinical plausibility and previous evidence. To examine the relationship between PEEP and extubation failure, a logistic regression model was developed using the median PEEP value across days 1, 3, and 7 for each patient. The median PEEP value was calculated, and this value was included as the primary predictor in the model. The following predictors were included in the model: age, gender, BMI, type of brain injury, GCS motor score at ICU admission, episode of anisocoria, and presence of visual pursuit. At extubation, the following predictors were included: GCS motor score the day of extubation, age, gender, PEEP before extubation, type of brain injury, ability to perform visual pursuit, ability to coughing (weak, moderate, vigorous), and cuff leak test. ARDS presence was also tested in a separate model as sensitivity analysis. PEEP was managed both as dichotomic and continuous variable. The overall model fit and the significance of individual coefficients were assessed, and variance inflation factors (VIF) were evaluated to detect multicollinearity among the independent variables. The logistic regression results were reported as odds ratios [OR] with 95 % confidence intervals [CIs], with predictor significance determined using the Wald test. For each model, we tested the inclusion of ICU site (center) as a random intercept using mixed-effects logistic regression to account for potential center-level variation in extubation practices. Model performance was compared using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

To assess the relationship between PEEP and ICU-mortality, a single Cox regression model was constructed using the median PEEP value across days 1, 3, and 7 for each patient. The following predictors were included based on clinical relevance: age, gender, GCS motor score, presence of visual pursuit, median PEEP across day 1,3,7, and episodes of anisocoria. The cumulative probability of survival was estimated using Kaplan-Meier survival curves. The log-rank test was applied to compare survival distributions between groups. Hazard ratios [HR] for each predictor were calculated, along with their corresponding 95 %CIs. The assumptions of proportional hazards were assessed using Schoenfeld residuals. Model fit was evaluated through concordance indices, and the null hypothesis estimate was reported. The significance of predictors within the Cox model was assessed using Z statistics, and *p*-values were derived from the Wald test. All statistical analyses were performed using JASP® software (version 0.19.3) and R® software, with a significance level set at $p < 0.05$ for all tests.

3. Results

3.1. General characteristics of the study cohort

Of the 1512 ENIO patients screened, 358 were excluded due to missing day-1 PEEP data and absence of extubation, leaving 1154 included: 485 (42 %) in the PEEP >5 cmH_2O group and 669 (58 %) in the PEEP ≤5 cmH_2O group at day 1. Median PEE*P* values [IQR] were 5 [IQR: 5–6] cmH_2O on day 1, 6 [IQR: 5–7] cmH_2O on day 3, 6 [IQR: 5–8] cmH_2O on day 7, and 5 [IQR: 5–6] cmH_2O at time of extubation (Fig. 1). Ventilatory settings and sedation practices at day 1 are shown in *SM Item S2*, while country-specific PEEP distributions are reported in *SM Item S3*.

Compared to the PEEP ≤5 cmH_2O group, patients in the PEEP >5 cmH_2O group had significantly higher BMI (27 [IQR: 23–29] vs. 25 [IQR: 22.5–28] kg/m^2, $p = 0.0016$), more ARDS during ICU stay (11.7 % vs. 6.8 %, $p = 0.0036$), less decompressive craniectomy (13.61 % vs. 17.96 %; $p = 0.0471$), and longer duration of invasive mechanical ventilation (median 8 [IQR: 4–15] days vs. 6 [IQR: 3–12] days; $p = 0.0158$), and ICU length of stay (median 14 [IQR: 7–25] days vs. 12 [IQR: 7–20] days; $p = 0.0018$). No significant differences were observed in the duration of non-invasive ventilation (median 2 [IQR: 1–4] days in both groups; $p = 0.8969$) or oxygen therapy (median 2 [IQR: 1–3] days in both groups; $p = 0.2065$). ICU mortality was 4.2 % in the higher PEEP group versus 3.3 % in the lower PEEP group ($p = 0.4441$), while in-hospital mortality was 8.1 % overall, with no differences between groups ($p = 0.9766$), see Table 1.

3.2. Association between PEEP and extubation failure

In the multivariable logistic regression model, higher median PEEP at days 1,3,7 (continuous variable) was significantly associated with increased odds of extubation failure (OR = 1.13, 95 %CI = 1.01–1.26, $p = 0.0294$). Age was an independent predictor of extubation failure, while the presence of TBI, visual pursuit, and higher GCS motor score were associated with decreased risk of extubation failure, see Table 2 *and SM Item S4*. When PEEP was modeled as a binary variable, PEEP>5 cmH_2O was no longer independently associated with an increased odds of extubation failure, see *SM Item S5*. In a posthoc analysis of main multivariable logistic regression model, we calculated the predicted probability of extubation failure across the full observed range of extubation PEEP while holding all other covariates at their mean or reference values and derived 95 %CI for each PEEP level, see Fig. 2. Including ICU site as a random intercept did not improve model fit for median PEEP at day 1,3,7, with degenerate estimates indicating negligible center-level variability, see *SM Item S6*.

At the time of extubation, median 7 days [IQR: 3–13.5], higher PEEP (continuous variable) was independently associated with an increased likelihood of extubation failure (OR = 1.13 95 %CI = 1.02–1.25, $p = 0.0218$), as well as the presence of weak cough (Table 3 *and SM Item S7)*. The presence of TBI and visual pursuit were associated with decreased risk of extubation failure. The results were confirmed when PEEP was modeled as a binary variable, with PEEP>5 cmH_2O remaining independently associated with an increased likelihood of extubation failure (*SM Item S8).* Adding ICU site as a random effect to the extubation PEEP model resulted in a singular fit, supporting the use of a fixed-effects model, see *SM Item S9.*

3.3. Sensitivity analysis in patients with ARDS

SM Item S10 shows the median PEEP values at days 1, 3, 7, and the day of extubation in patients with and without ARDS. PEEP levels were significantly higher in patients with ARDS than those without ARDS at all time points. PEEP values, stratified according to the severity of ARDS (mild, moderate, severe), are reported in *SM Item S11*. In the sensitivity multivariate logistic regression analysis including ARDS as a covariate, median PEEP at day 1,3,7 was no longer significantly associated with extubation failure; however, the presence of ARDS during ICU stay was independently associated with higher odds of extubation failure (OR = 2.51 95 %CI = 0.44–1.40, $p < 0.001$), *SM Item S12*.

After adjusting for the presence of ARDS, higher PEEP at extubation was no longer associated with extubation failure; however, the presence of ARDS during ICU stay was independently associated with higher odds of extubation failure (OR = 2.10 95 %CI = 0.23–1.25, $p = 0.0043$), *SM Item S13*.

3.4. Association between PEEP and ICU-mortality

Median PEEP at days 1, 3, 7 (continuous variable) was not associated with ICU-mortality. However, age and the inability to perform visual pursuit were associated with an increased hazard of ICU-mortality, see *SM Item S14*. When PEEP was modeled as binary variable, the non-association with ICU-death was consistent, *SM Item S15*. Kaplan—Meier curves for survival in the overall cohort and according to PEEP as binary variable are reported in Fig. 3.

Higher levels of PEEP the day of extubation (continuous variable) were independently associated with increased ICU-mortality risk (HR = 1.38 95 %CI = 1.12–1.69, $p = 0.0026$). Higher patient age was also associated with an increased risk of death, while a higher GCS motor

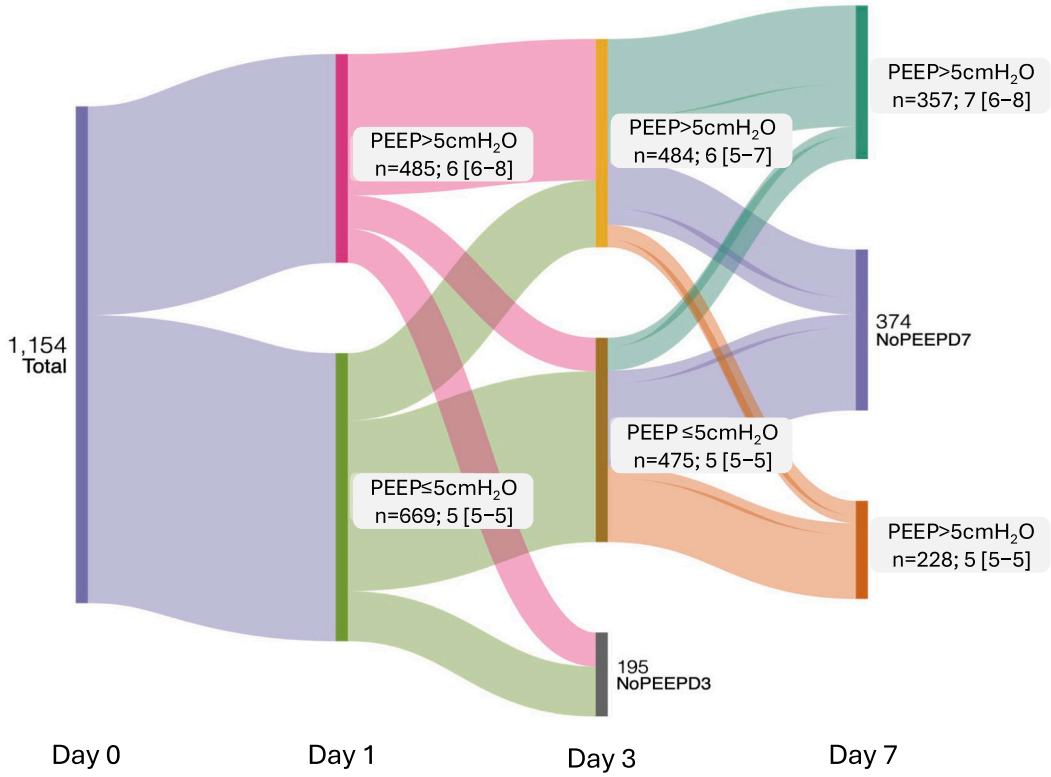

Fig. 1. Sankey plot (alluvional plot) for PEEP distribution over Days.
Number of patients with available PEEP data are reported over Days with respective median (25th—75th percentiles) PEEP values at each timepoint (Day 0 = Intensive Care Unit admission, 1, 3, 7). The figure was done with the online free software SankeyMATIC ®.

score at extubation, and the presence of visual pursuit were significantly associated with lower risk of death, see *SM Item S16*. When PEEP was modeled as binary variable, the association with ICU-death was lost, *SM Item S17*.

4. Discussion

The findings of this study can be summarized as follows: (a) PEEP levels in patients with ABI remained around 5–6 cmH_2O throughout their ICU stay, with minimal variability across countries; (b) higher PEEP levels at extubation (and specifically >5 cmH_2O) and median of PEEP at day 1,3,7 were independently associated with an increased likelihood of extubation failure and the presence of ARDS; (c) ICU mortality was associated with PEEP levels at extubation, but not median of PEEP at days 1,3,7; (d) the presence of ARDS during ICU stay was independently associated with increased risk of extubation failure, regardless of PEEP level.

The main strengths of this study are the robust methodology and extensive data collection as part of the ENIO study [2], an international multicenter cohort, with high-quality and comprehensive data collection, enhancing the reliability of findings. The inclusion of a large and diverse cohort of ABI patients improves the generalizability of results across various clinical settings. Furthermore, the use of advanced statistical modeling, including logistic regression and Cox proportional hazards models, allows for a more nuanced understanding of the relationship between PEEP, extubation failure, and mortality.

4.1. General characteristics of the study cohort

Our study aligns with the IMV trends of the last decade in ABI patients, suggesting a global effort to standardize IMV strategies in this population. As reported by Tejerina et al., in 2004, PEEP was kept <5 cmH_2O in 72 % and between 5 and 10 cmH_2O in 24 % of patients. By 2010, these proportions shifted to 58 % and 36 % of patients, respectively, and by 2016, to 56 % and 40 % of patients, respectively [4]. Our findings, reflecting IMV practices from 2017 to 2020, indicate a continued trend toward increasing PEEP levels over time, in agreement with lung-protective IMV strategies. However, recent data from the PROLABI trial (2024), challenge the assumption that higher PEEP levels are beneficial in ABI patients. This trial compared a lung-protective ventilatory strategy—characterized by lower tidal volumes and higher PEEP levels—to a conventional ventilatory approach. The lung-protective strategy was associated with increased mortality, a lower rate of IMV weaning, a higher incidence of ARDS, and poorer neurological outcomes [10]. In our study, higher PEEP levels likely reflect the management of respiratory complications such as ARDS, which was present in 9.2 % of patients. In line with current ARDS guidelines [3,9,17,18], patients with more severe lung injury at admission may require higher PEEP levels to improve oxygenation and lung recruitment. In accordance with previous findings, patients who received higher PEEP also had concomitantly lower tidal volumes and higher respiratory rates [19]. Our results highlight the need for a personalized approach when applying lung-protective IMV settings in ABI patients. While higher PEEP may benefit lung function, its potential physiological effects on cerebral hemodynamics must be carefully considered. These findings underscore the importance of individualized ventilatory strategies tailored to the patient's underlying pathology.

4.2. Association between PEEP and extubation failure

While PEEP is known to improve oxygenation by recruiting collapsed alveoli [5], our findings indicate that each 1 cmH_2O increase in PEEP on the day of extubation raises the odds of extubation failure by approximately 13 % (OR = 1.13 95 %CI = 1.02–1.25, $p = 0.0218$). Particularly, for PEEP >5 cmH_2O the risk of extubation failure is confirmed. Similarly, the WEAN-SAFE study found a 6 % increase in weaning failure

Table 1
Baseline characteristics, demographics, and ICU outcomes of the overall population and according to the PEEP value at ICU Day 1.

	Overall $n = 1154$	PEEP > 5 cmH_2O $n = 485$	PEEP ≤ 5 cmH_2O $n = 669$	P-value
Demographics				
Age, years, median [25th; 75th]	54 [36; 66]	54 [37; 65]	54 [35; 66]	0.6604
Gender, n (%)				0.6850
Male	780 (67.59)	331 (68.25)	449 (67.12)	
Female	374 (32.41)	154 (31.75)	220 (32.88)	
BMI, kg/m^2, median [25th; 75th]	25 [23; 29]	27 [23; 30]	25 [22.5; 28]	0.0016
Country, n (%)				
Argentina	41 (3.55)	4 (0.82)	37 (5.53)	<0.001
Bangladesh	2 (0.17)	0 (0.00)	2 (0.30)	
Belgium	18 (1.56)	0 (0.00)	18 (2.69)	
Canada	12 (1.04)	2 (0.41)	10 (1.49)	
France	607 (52.60)	257 (52.99)	350 (52.32)	
Greece	14 (1.21)	4 (0.82)	10 (1.49)	
India	19 (1.65)	6 (1.24)	13 (1.94)	
Italy	56 (4.85)	33 (6.80)	23 (3.44)	
Japan	19 (1.65)	11 (2.27)	8 (1.20)	
Libyan	8 (0.69)	5 (1.03)	3 (0.45)	
Mexico	145 (12.56)	68 (14.02)	77 (11.51)	
Netherlands	45 (3.90)	15 (3.09)	30 (4.48)	
Qatar	11 (0.95)	2 (0.41)	9 (1.34)	
Switzerland	63 (5.46)	31 (6.39)	32 (4.78)	
United Kingdom	44 (3.81)	15 (3.09)	29 (4.33)	
United States	5 (0.43)	0 (0.00)	5 (0.75)	
Uruguay	27 (2.34)	25 (5.15)	2 (0.30)	
Baseline comorbidities				
Pulmonary disease, n (%)	44 (3.82)	22 (4.55)	22 (3.29)	0.2716
Heart Failure, n (%)	36 (3.12)	16 (3.31)	20 (2.99)	0.7606
Hypertension, n (%)	340 (29.49)	145 (29.90)	195 (29.15)	0.7658
Active smoking, n (%)	252 (21.99)	106 (21.99)	146 (21.99)	0.9988
Diabetes mellitus, n (%)	133 (11.54)	63 (13.02)	70 (10.46)	0.1805
History of malignancy, n (%)	52 (4.51)	23 (4.75)	29 (4.33)	0.7362
Cause of ICU admission				
TBI, n (%)	569 (49.31)	230 (47.42)	339 (50.67)	0.2757
ICH, n (%)	375 (32.50)	152 (31.34)	223 (33.33)	0.4755
SAH, n (%)	204 (17.68)	90 (18.56)	114 (17.04)	0.5051
Ischemic Stroke, n (%)	102 (8.84)	44 (9.07)	58 (8.67)	0.8121
CNS infection, n (%)	50 (4.33)	24 (4.95)	26 (3.89)	0.3817
Brain Tumor, n (%)	61 (5.29)	30 (6.19)	31 (4.63)	0.2449
Other, n (%)	20 (1.73)	7 (1.44)	13 (1.95)	0.5186
Neurologic characteristics				
GCS total, mean (SD) median [25th; 75th]	6.99 (2.63) 7 [5; 9]	6.89 (2.62) 7 [5; 9]	7.05 (2.63) 7 [5; 9]	0.3089
Anisocoria, n (%)	299 (25.98)	127 (26.29)	172 (25.75)	0.8350
Intracranial probe, n (%)	523 (45.40)	219 (45.15)	304 (45.58)	0.8869
EVD, n (%)	337 (29.23)	137 (28.25)	200 (29.94)	0.5327
Posterior fossa injury, n (%)	66 (5.73)	25 (5.17)	41 (6.14)	0.4833
Therapeutic hypothermia, n (%)	47 (4.08)	23 (4.74)	24 (3.59)	0.3299
Barbiturate coma, n (%)	58 (5.03)	28 (5.77)	30 (4.49)	0.3254
Neurosurgery, n (%)	437 (37.90)	184 (37.94)	253 (37.87)	0.9824
Decompressive craniectomy, n (%)	186 (16.13)	66 (13.61)	120 (17.96)	0.0471
ICU outcome				
VAP, n (%)	434 (37.94)	196 (40.92)	238 (35.79)	0.0778
Tracheobronchitis, n (%)	107 (9.41)	51 (10.71)	56 (8.47)	0.2014
ARDS, n (%)	101 (8.84)	56 (11.72)	45 (6.77)	0.0036
Reintubation, n (%)	243 (21.24)	111 (23.13)	132 (19.88)	0.1853
Tracheostomy required, n (%)	93 (8.16)	45 (9.45)	48 (7.23)	0.1759
IMV duration, days, median [25th; 75th]	7 [3; 13.5]	8 [4; 15]	6 [3; 12]	0.0158
Non-IMV duration, days, median [25th; 75th]	2 [1; 4]	2 [1; 4]	2 [1; 5]	0.8969
Oxygen duration, days, median [25th; 75th]	2 [1; 3]	2 [1; 3]	2 [1; 3]	0.2065
ICU LOS, days, median [25th; 75th]	13 [7; 22]	14 [7; 25]	12 [7; 20]	0.0018
In-ICU mortality, n (%)	42 (3.70)	20 (4.20)	22 (3.33)	0.4441
In-hospital mortality, n (%)	91 (8.10)	38 (8.07)	53 (8.12)	0.9766

Data are reported as median (interquartile range, IQR) for standardization in reporting. P values are calculated using the t-tests or Mann-Whitney U tests, and the Chi-square test as appropriate. BMI = body mass index; TBI = traumatic brain injury; ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage; CNS = central nervous system; GCS = Glasgow coma scale; EVD = external ventricular derivation; VAP = ventilator-associated pneumonia; ARDS = acute respiratory distress syndrome; IMV = invasive mechanical ventilation; ICU = intensive care unit; LOS = length of stay.

Table 2
Logistic regression: predictors of extubation failure (median PEEP day 1,3,7 as primary predictor).

Variable	OR (95 % CI)	p-value
Median PEEP day 1,3,7 (cmH_2O)	1.13 (1.01–1.26)	0.0294
Patient age (years)	1.01 (1.00–1.02)	0.0436
GCS motor score at ICU admission	0.96 (0.82–0.98)	0.0224
BMI (kg/m^2)	1.00 (0.96–1.03)	0.7866
Traumatic Brain Injury	0.54 (0.37–0.78)	0.0010
Intracranial Hemorrhage	1.34 (0.96–1.86)	0.0861
Visual pursuit	0.68 (0.47–0.98)	0.0395
Gender (female)	0.79 (0.56–1.11)	0.1757
Episode of anisocoria	1.00 (0.70–1.41)	0.9790
Aneurysmal hemorrhage	0.81 (0.52–1.25)	0.3324

Extubation failure coded as (1); OR = odds ratio; CI = confidence interval; BMI = body mass index; GCS = Glasgow Coma Scale.

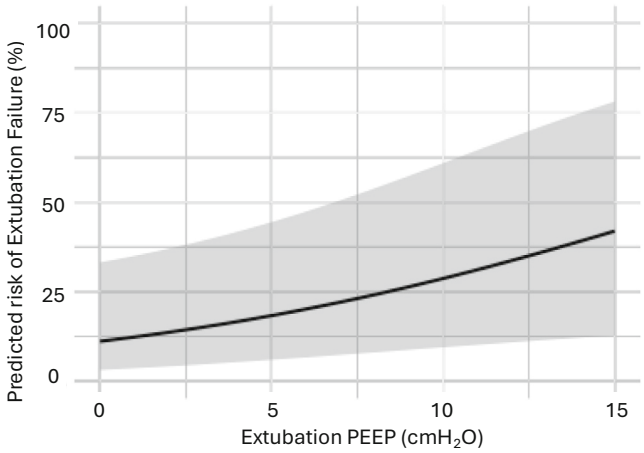

Fig. 2. Predicted probability of extubation failure across extubation PEEP levels with 95 % confidence intervals from multivariable logistic regression.
Predicted probability of extubation failure across the observed range of extubation PEEP levels (cmH_2O), derived from the multivariable logistic regression model in a posthoc analysis. All other covariates were held at their mean (continuous variables) or reference (categorical variables) values. The solid curve represents the predicted risk of extubation failure, while the shaded area indicates the 95 % confidence interval. The y-axis represents the predicted probability expressed as a percentage.

Table 3
Logistic regression: predictors of extubation failure (PEEP at extubation as primary predictor).

Variable	OR (95 % CI)	p-value
PEEP at extubation (cmH_2O)	1.13 (1.02–1.25)	0.0218
Traumatic Brain Injury	0.47 (0.32–0.68)	0.0010
Intracranial Hemorrhage	1.26 (0.89–1.77)	0.1933
Cuff leak test	0.97 (0.69–1.37)	0.8724
Visual pursuit	0.65 (0.43–0.98)	0.0389
Cough none	3.24 (0.85–12.32)	0.0839
Cough weak	2.30 (0.62–8.50)	0.2107
Cough vigorous	1.38 (0.37–5.15)	0.6303
Patient age (years)	1.00 (0.99–1.01)	0.4928
GCS motor score at extubation	0.96 (0.79–1.18)	0.7075
Gender (female)	0.77 (0.54–1.10)	0.1538

Extubation failure coded as (1); OR = odds ratio; CI = confidence interval; GCS = Glasgow Coma Scale.

odds per 1 cmH_2O rise in PEEP (OR = 1.06, 95 % CI = 1.0–1.11, p = 0.036). After excluding 1079 patients with neurological conditions, the association remained consistent, with a 7 % increase in weaning failure odds per 1 cmH_2O increment in PEEP. These findings highlight the potential risks of higher PEEP levels at extubation, underscoring the importance of reassessing PEEP before discontinuing mechanical ventilation [20].

The impact of PEEP on extubation failure may be exacerbated in patients with hemodynamic instability, particularly if the increased work of breathing post-extubation is underestimated [21–24]. Our analysis revealed significant associations between median PEEP at days 1, 3, and 7 and extubation failure, suggesting that not only the level but also the duration of exposure to elevated PEEP—or the "dose" of PEEP over the recovery period—may be critical. This appears particularly relevant for ABI patients, who may have altered respiratory drive and impaired airway reflexes, making them more vulnerable to the prolonged effects of high PEEP [2,25].

Weaning from invasive mechanical ventilation in ABI patients typically considers the patient's neurological status, ventilator settings, physiological parameters, and clinical judgment, often preceded by a spontaneous-breathing trial (SBT) [26]. Various SBT techniques exist, ranging from pressure-support ventilation to non-assisted methods [27,28]. A recent protocol reported that using a 10-15 cmH_2O of positive pressure during cuff deflation improves weaning success [29,30]. A meta-analysis comparing positive-pressure and suctioning techniques suggested that positive-pressure weaning was associated with a lower, albeit not statistically significant, risk of complications including desaturation, airway obstruction, pneumonia, aspiration, atelectasis, and reintubation [31]. Considering the worldwide variability in weaning practice, the ideal ventilator settings, including PEEP and pressure support levels during SBT and extubation, is a topic of continuous debate [20,26].

Brain injury presents significant challenges during the weaning and extubation phases [2]. In ABI patients, reintubation rates are approximately 21 % after extubation. Strong predictors of extubation success include TBI, vigorous cough, intact gag reflex, and a GCS motor score of 6. Although recent studies, including the ENIO study, explore the impact of different ventilatory strategies on weaning success in ABI patients, the role of PEEP remains uncertain [2]. PEEP significantly affects brain physiology and cerebral hemodynamics, particularly in patients with compromised cerebral autoregulation, increasing vulnerability to perfusion variations [7,32–35], contributing to cerebral hemodynamics and ICP [36,37].

Interestingly, preserved cognitive function, such as the ability to track objects visually, appears to be a protective factor against extubation failure, suggesting that better neurological status enhances weaning success [6,38–40]. Evidence supports using cognitive and motor assessments to determine extubation readiness, emphasizing the need for individualized weaning protocols based on neurological evaluations [2]. This highlights the importance of a multidisciplinary approach in managing ABI patients, involving intensivists, neurologists, neurosurgeons, and respiratory therapists.

In patients with ARDS, our data suggest that higher PEEP at the time of extubation is not independently associated with extubation failure. Instead, it is the presence of ARDS itself that confers a higher risk. This may reflect the fact that elevated PEEP is often necessary in ARDS to maintain adequate oxygenation and alveolar recruitment and does not independently worsen outcomes when used appropriately. Conversely, the pathophysiological severity of ARDS—rather than PEEP per se—may compromise respiratory mechanics, gas exchange, and the success of extubation [41,42].

4.3. Association between PEEP and ICU-Mortality

Median PEEP at day 1,3,7 was not associated with ICU mortality; however, higher PEEP levels at extubation were associated with an increased risk of ICU mortality. Specifically, each 1 cmH_2O increase in PEEP at extubation was associated with a 38 % rise in the hazard of ICU mortality. This was not confirmed for PEEP >5 cmH_2O when dichotomizing PEEP into two groups, suggesting a dose-response relationship may be more informative than binary thresholds. This finding underscores a limitation of categorical thresholds in ventilatory decision-making. A cutoff such as >5 cmH_2O may fail to capture the gradual and cumulative risk associated with increasing PEEP levels, especially at the time of extubation when patients may be more vulnerable to the hemodynamic and respiratory consequences of elevated intrathoracic pressure and ICP [6,9,33]. It also suggests that patients with only moderately elevated PEEP may still carry increased risk, which is masked when grouped with lower-risk individuals under a single binary definition. Rather than relying on arbitrary cutoffs, these results support a continuous and individualized interpretation of PEEP values, especially in the context of extubation readiness. PEEP at this stage may reflect unresolved lung injury or ongoing ARDS, which could independently contribute to poor outcomes. A nuanced approach that accounts for both the absolute level and trajectory of PEEP, rather than fixed thresholds, may improve risk stratification and guide safer weaning practices [43,44]. The demographics of the study population show a

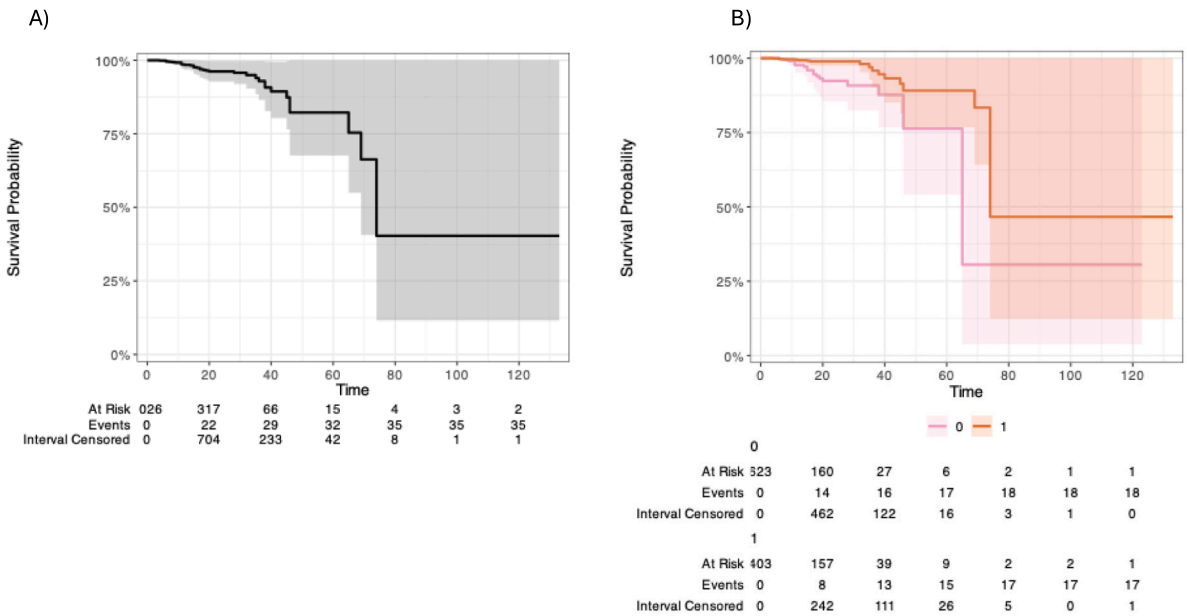

Fig. 3. ICU Survival Probability Over Time: Overall and Stratified by Extubation PEEP Levels.
A) Kaplan–Meier survival curve showing ICU survival probability over time. The curve incorporates interval-censored data and displays the number of events and patients at risk at each time point. Survival probability is shown on the y-axis, and time (in days) on the x-axis. B) Kaplan–Meier survival curves stratified by a binary variable (stratum PEEP<5 cmH_2O vs PEEP≥5 cmH_2O), showing ICU survival probability over time. The plot displays interval-censored events and the number of patients at risk at successive time points for each stratum. Survival probability is plotted on the y-axis, and time (in days) on the x-axis. Shaded areas represent confidence intervals.

mean age of 52 years with a predominance of males. Increased age, lower GCS motor score at extubation, and the inability to perform visual pursuits were independently associated with increased ICU-mortality, emphasizing the need for comprehensive assessments beyond ventilatory settings [5,8,31].

4.4. Limitations

Despite its strengths, the study has limitations. The retrospective nature of the post-hoc analysis may introduce bias, as the original study design did not specifically intend to investigate the relationship between PEEP levels and extubation failure. Additionally, the variability in clinical practices across different centers may affect the consistency of PEEP application and monitoring. The observational design also limits the ability to draw causal inferences, and confounding variables, despite adjustments, may still influence the results. Moreover, due to the structure of the original ENIO dataset, we could not account for potential confounding conditions such as pneumonia, pulmonary embolism, or cardiac injury, which may have influenced extubation outcomes. A key analytical limitation is the use of binary categorization for PEEP levels (e.g., >5 cmH_2O vs. ≤5 cmH_2O), which may obscure clinically relevant dose-response effects. The absence of an association when PEEP is dichotomized, despite a significant effect when modeled as a continuous variable, highlights the potential loss of granularity and sensitivity inherent in threshold-based approaches. Moreover, while higher PEEP levels were associated with extubation failure, this relationship may reflect underlying disease severity—particularly the presence of ARDS—rather than a direct causal effect, highlighting the potential for residual confounding despite multivariable adjustment. Unfortunately, the cause of extubation failure was frequently missing in the ENIO dataset, precluding reliable subgroup analyses by airway vs non-airway failure. Finally, the absence of long-term outcome data post-ICU discharge may limit our understanding of the overall impact of PEEP on patient neurological recovery and quality of life.

5. Conclusions

Our results indicate that elevated PEEP levels at extubation are associated with a higher risk of extubation failure and ICU mortality; however, this association is not independent of ARDS. Instead, the presence of ARDS during ICU stay emerged as a key driver of extubation failure. These findings suggest that PEEP may act more as a surrogate marker of underlying disease severity rather than as a direct causal factor.

List of ENIO Collaborators

First Name	Last Name	Center
Paër-Sélim	Abback	Department of Anesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP.Nord, Paris, France.
Anaïs	Codorniu	Department of Anesthesiology and Critical Care, Beaujon Hospital, DMU Parabol, AP-HP.Nord, Paris, France.
Giuseppe	Citerio	Neurointensive Care Unit, Ospedale San Gerardo Monza, Italy University of Milano-Bicocca, Monza, Italy
Vittoria Ludovica	Sala	Neurointensive Care Unit, Ospedale San Gerardo Monza, Italy University of Milano-Bicocca, Monza, Italy
Marinella	Astuto	Anesthesia and Intensive Care Unit, A.O.U. Policlinico "G. Rodolico - S. Marco"
Eleonora	Tringali	Anesthesia and Intensive Care Unit, A.O.U. Policlinico "G. Rodolico - S. Marco"
Daniela	Alampi	Sapienza Rome University, A.O.U. Sant'Andrea
Monica	Rocco	Sapienza Rome University, A.O.U. Sant'Andrea
Jessica Giuseppina	Maugeri	Arnas Garibaldi Catania
Agrippino	Bellissima	Arnas Garibaldi Catania

(continued on next page)

(*continued*)

First Name	Last Name	Center
Matteo	Filippini	University Division of Anesthesiology and Critical Care Medicine, ASST Spedali Civili, Brescia, Italy
Nicoletta	Lazzeri	University Division of Anesthesiology and Critical Care Medicine, ASST Spedali Civili, Brescia, Italy
Andrea	Cortegiani	Policlinico Paolo Giaccone, Università degli Studi di Palermo
Mariachiara	Ippolito	Policlinico Paolo Giaccone, Università degli Studi di Palermo
Chiara	Robba	Ospedale Policlinico San Martino, Genoa, Italy; Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Italy
Denise	Battaglini	Ospedale Policlinico San Martino, Genoa, Italy; Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Italy
Pasquale	Anania	Ospedale Policlinico San Martino, Genoa, Italy
Gianluigi	Zona	Ospedale Policlinico San Martino, Genoa, Italy
Patrick	Biston	CHU Charleroi- Hôpital Civil Marie-Curie
Mohamed Fathi	Al-Gharyani	Benghazi Medical Center
Russell	Chabanne	Clermont-Ferrand University Hospital, Neurocritical Care Unit, Perioperative Medicine Department
Léo	Astier	Clermont-Ferrand University Hospital, Neurocritical Care Unit, Perioperative Medicine Department
Benjamin	Soyer	AP-HP, Hôpital Lariboisière, Department of Anesthesia and Critical Care, DMU Parabol, Paris, France
Samuel	Gaugain	AP-HP, Hôpital Lariboisière, Department of Anesthesia and Critical Care, DMU Parabol, Paris, France
Alice	Zimmerli	Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern
Urs	Pietsch	Department of Anaesthesiology and Intensive Care Medicine, Cantonal Hospital St Gallen
Miodrag	Filipovic	Department of Anaesthesiology and Intensive Care Medicine, Cantonal Hospital St Gallen
Giovanna	Brandi	Institute for Intensive Care Medicine, *University Hospital* of Zurich
Giulio	Bicciato	Institute for Intensive Care Medicine, *University Hospital* of Zurich
Ainhoa	Serrano	Hospital Clinico Universitario Valencia
Berta	Monleon	Hospital Clinico Universitario Valencia
Peter	van Vliet	Haaglanden Medical Center
Benjamin Marcel	Gerretsen	Haaglanden Medical Center
Iris Xochitl	Ortiz-Macias	Hospital Civil de Guadalajara "Fray Antonio Alcalde"
Jun	Oto	Tokushima University Hospital
Noriya	Enomoto	Tokushima Prefectural Central Hospital
Tomomichi	Matsuda	Sapporo Higashi Tokushukai Hospital
Nobutaka	Masui	Sapporo Higashi Tokushukai Hospital
Pierre	Garçon	Service de réanimation
Jonathan	Zarka	Service de réanimation
Wytze J.	Vermeijden	Dep of intensive care, Medisch Spectrum Twente MST, Enschede, the Netherlands
Alexander Daniel	Cornet	Dep of intensive care, Medisch Spectrum Twente MST, Enschede, the Netherlands
Sergio Reyes	Inurrigarro	UMAE Hospital de Traumatologia y Ortopedia IMSS
Rafael Cirino Lara	Domínguez	UMAE Hospital de Traumatologia y Ortopedia IMSS
Maria Mercedes	Bellini	Hospital Maciel
Maria Milagros	Gomez Haedo	Hospital Maciel
Laura	Lamot	Hospital Municipal Leonidas Lucero
Jose	Orquera	Sanatorio Pasteur
Matthieu	Biais	Pellegrin SAR Tripode
Delphine	Georges	Pellegrin SAR Tripode

(*continued on next column*)

(*continued*)

First Name	Last Name	Center
Arvind	Baronia	Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow
Roberto Carlos	Miranda-Ackerman	Hospital San Javier
Francisco José	Barbosa-Camacho	Hospital San Javier
John	Porter	St George's Hospital
Miguel	Lopez-Morales	St George's Hospital
Thomas	Geeraerts	Toulouse University Hospital
Baptiste	Compagnon	Toulouse University Hospital
David	Pérez-Torres	Servicio de Medicina Intensiva, Hospital Universitario Río Hortega
Estefanía	Prol-Silva	Servicio de Medicina Intensiva, Hospital Universitario Río Hortega
Hana Basheer	Yahya	Zliten medical centre
Ala	Khaled	Abo Selim Trauma Hospital
Mohamed	Ghula	Abo Selim Trauma Hospital
Cracchiolo Neville	Andrea	Terapia Intensiva Con Trauma Center Arnas Ospedale Civico Palermo
Palma Maria	Daniela	Terapia Intensiva Con Trauma Center Arans Ospedale Civico Palermo
Cristian	Deana	Academic Hospital of Udine
Luigi	Vetrugno	University of Chieti-Pescara
Manuel J. Rivera	Chavez	Hospital de Alta Especialidad del Bajio
Rocio Mendoza	Trujillo	Hospital de Alta Especialidad del Bajio
Vincent	Legros	Department of Anesthesiology and Critical Care, University Hospital of Reims
Benjamin	Brochet	Department of Anesthesiology and Critical Care, University Hospital of Reims
Olivier	Huet	Department of Anesthesiology and Critical Care, La Cavale Blanche
Marie	Geslain	Department of Anesthesiology and Critical Care, La Cavale Blanche
Mathieu	Van der Jagt	Erasmus MC Rotterdam
Job	Van Steenkiste	Erasmus MC Rotterdam
Hazem	Ahmed	Seoul Clinic
Alexander Edward	Coombs	University Hospital Plymouth
Jessie	Welbourne	University Hospital Plymouth
Ana Alicia	Velarde Pineda	Hospital General Regional # 180 IMSS
Víctor Hugo	Nubert Castillo	Hospital General Regional # 180 IMSS
Mohammed A	Azab	Cairo University
Ahmed Y	Azzam	Cairo University
David Michael Paul	van Meenen	Amsterdam UMC
Gilberto Adrian	Gasca	Hospital Regional de Alta Especialidad de Ixtapaluca
Alfredo	Arellano	Hospital Regional de Alta Especialidad de Ixtapaluca
Forttino	Galicia-Espinosa	UMAE Hospital de Traumatología y Ortopedia No 21, IMSS Monterrey
José Carlos	García-Ramos	UMAE Hospital de Traumatología y Ortopedia No 21, IMSS Monterrey
Ghanshyam	Yadav	Trauma ICU, Department of Anesthesia, IMS, BHU
Amarendra Kumar	Jha	Trauma ICU, Department of Anesthesia, IMS, BHU
Vincent	Robert-Edan	Nantes-Laennec
Pierre-Andre	Rodie-Talbere	Nantes-Laennec
Gaurav	Jain	Critical Care Unit, Dept. Of Anaesthesiology and Critical Care, All India Institute of Medical Sciences Rishikesh
Sagarika	Panda	Critical Care Unit, Dept. Of Anaesthesiology and Critical Care, All India Institute of Medical Sciences Rishikesh
Sonika	Agarwal	HIMS
Yashbir	Deewan	HIMS
Gilberto Adrian	Gasca	Hospital Regional de Alta Especialidad de Ixtapaluca
Alfredo	Arellano	Hospital Regional de Alta Especialidad de Ixtapaluca
Syed Tariq	Reza	Dhaka Medical College Hospital
Md. Mozaffer	Hossain	Dhaka Medical College Hospital
Christos	Papadas	ICU of asklepieio G.H.A
Vasiliki	Chantziara	Saint Savvas hospital
Chrysanthi	Sklavou	Saint Savvas hospital

(*continued on next page*)

(*continued*)

First Name	Last Name	Center
Yannick	Hourmant	Department of Anesthesiology and Critical Care, Hôtel-Dieu, Nantes, France
Nicolas	Grillot	Department of Anesthesiology and Critical Care, Hôtel-Dieu, Nantes, France
Job	van Steenkiste	Erasmus Medical Centre
Mathieu	van der Jagt	Erasmus Medical Centre
Romain	Pirracchio	Department of Anesthesia and Perioperative Care, University of California, UCSF
Abdelraouf	Akkari	Qatar-1
Mohamed	Abdelaty	Qatar-2
Ahmed	Hashim	Qatar-2
Yoann	Launey	Department of Anesthesiology and Critical Care, Hopital Pontchaillou, France
Elodie	Masseret	Department of Anesthesiology and Critical Care, Hopital Pontchaillou, France
Sigismond	Lasocki	Department of Anesthesiology and Critical Care, Angers, France
Soizic	Gergaud	Department of Anesthesiology and Critical Care, Angers, France
Nicolas	Mouclier	Department of Anesthesiology and Critical Care, Hôtel-Dieu, Nantes, France
Sulekha	Saxena	King George's Medical University
Avinash	Agrawal	King George's Medical University
Shakti Bedanta	Mishra	IMS and SUM Hospital
Samir	Samal	IMS and SUM Hospital
Julio Cesar	Mijangos	Hospital Civil de Guadalajara "Fray Antonio Alcalde" Hospital No. 278
Mattias	Haënggi	Inselspital, Bern University Hospital
Mohan	Gurjar	Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS)
Marcus J.	Schultz	Department of Intensive Care, Amsterdam University Medical Centers
Callum	Kaye	Aberdeen Royal Infirmary
Daniel Agustin	Godoy	Sanatorio Pasteur
Pablo	Alvarez	Hospital Maciel
Aikaterini	Ioakeimidou	Asklepieio G.H.A
Yoshitoyo	Ueno	Tokushima University Hospital
Rafael	Badenes	Hospital Clínico Universitario Valencia
Abdurrahmaan	Suei Elbuzidi	Qatar-1
Michaël	Piagnerelli	Hôpital Civil Marie-Curie, Université libre de Bruxelles
Muhammed	Elhadi	Faculty of Medicine, University of Tripoli, Furnaj
Syed Tariq	Reza	Dhaka Medical College Hospital
Mohammed Atef	Azab	Cairo University
Jean Catherine	Digitale	University of California
Nicholas	Fong	University of California
Ricardo Campos	Cerda	Critical Care Unit, Hospital General Regional no. 46, Instituto Mexicano del Seguro Social
Norma de la Torre	Peredo	Critical Care Unit, Hospital General Regional no. 46, Instituto Mexicano del Seguro Social
Romain	Pirracchio	University of California
Robert David	Stevens	University of John Hopkins

CRediT authorship contribution statement

Denise Battaglini: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Raphael Cinotti:** Writing – review & editing, Visualization, Validation, Investigation, Data curation. **Karim Asehnoune:** Writing – review & editing, Visualization, Validation, Investigation, Data curation. **Andrea Loggini:** Writing – review & editing, Visualization, Validation. **Luca Montagnani:** Writing – review & editing, Visualization, Validation. **Lorenzo Ball:** Writing – review & editing, Visualization, Validation, Methodology. **Francesca Gualdi:** Writing – review & editing, Visualization, Validation. **Patricia R.M. Rocco:** Writing – review & editing, Visualization, Validation, Supervision. **Marcus J. Schultz:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation. **Nicolò Antonino Patroniti:** Writing – review & editing, Visualization, Validation, Investigation. **Chiara Robba:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7/11/2017, provided the initial permission. The local ethics committees at each participating center granted permission to conduct the ENIO study. In accordance with local laws and regulations, both written and verbal informed consent was given to participate in the ENIO study.

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Declaration of competing interest

The author Denise Battaglini (DB) declares lecturer for ESTOR, not related to this work. The author Chiara Robba (CR) declares consulting or advisory for DB, not related to this work. The other authors declare no competing financial interests or personal relationships. All authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2025.155274.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

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Glossary

ABI: Acute Brain Injury
ARDS: Acute Respiratory Distress Syndrome
BMI: Body Mass Index
CI: Confidence Interval
CNS: Central Nervous System
CPP: Cerebral Perfusion Pressure
ENIO: Extubation strategies in Neuro-Intensive care unit patients, and associations with Outcomes
EVD: External Ventricular Drainage
FiO_2: fraction of inspired oxygen
GCS: Glasgow Coma Score
HR: Hazard Ratio
LOS: Length of Stay
ICH: Intracranial Hemorrhage
ICP: Intracranial Pressure

IMV: Invasive Mechanical Ventilation
IQR: Interquartile Range
IS: Ischemic Stroke
OR: Odds Ratio
$PaCO_2$, mmHg: arterial partial pressure of carbon dioxide
PaO_2: Arterial Partial Pressure of Oxygen
PBW: Predicted Body Weight
PEEP: Positive End-Expiratory Pressure
pHa: arterial pH
SAH: Subarachnoid Hemorrhage
SD: Standard Deviation
SpO_2: Saturation of Peripheral Oxygen
TBI: Traumatic Brain Injury
VAP: Ventilator-Associated Pneumonia
VIF: Variance Inflation Factors