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Association of age with extubation failure in neurocritical intensive care unit patients—Insight from an international prospective study named ENIO

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ABSTRACT

Objective: To assess the association of age with extubation failure in neurocritical care patients.
Design: Posthoc analysis of the ‘Extubation strategies in Neuro–Intensive care unit patients and associations with Outcomes (ENIO) study’, an international prospective observational study.
Setting: ENIO was conducted in 73 centers in 18 countries from 2018 to 2020.
Patients: Neurocritical care patients with a Glasgow Coma Scale score $\leq$ 12 and receiving ventilation for at least 24 h were included. We categorized patients into four age groups based on age quartiles.
Main results: This analysis included 1095 patients with a median age of 53 [35 to 65] years. Younger patients were more likely to be admitted with traumatic brain injury, whereas older patients more often had cerebral hemorrhage, ischemic stroke, central nervous infection, or brain malignancies. Extubation failure occurred in 209 (19 %) patients. In the unadjusted analysis, older patients had a higher risk of extubation failure (odds ratio (OR), 1.012 [95 %–confidence interval (CI) 1.004 to 1.021]; $P = 0.006$). However, after adjusting for confounding factors, the effect of age on extubation failure was no longer significant (OR, 1.008 [0.997 to 1.019]; $P = 0.172$).
Conclusions: In this international cohort of intubated and ventilated neurocritical care patients, after adjusting for baseline covariates and for previously identified risk factors for extubation failure, age was not associated with extubation failure. Age may not be a factor to consider in extubation decisions for brain–injured patients.
Registration: ENIO is registered at clinicaltrials.gov (study identifier NCT 03400904).

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[1] ENIO, ‘Extubation strategies in Neuro–Intensive care unit patients and associations with Outcomes study’

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1. Introduction

Neurocritical care patients frequently require prolonged invasive ventilation [1]. This can arise for various reasons, including a decreased level of consciousness, impaired airway protective reflexes, impaired respiratory drive, recurrent seizures or status epilepticus, and secondary pulmonary complications such as aspiration, pneumonia, pulmonary edema and even the acute respiratory distress syndrome (ARDS) [2–4]. Extubation failure often occurs in neurocritical care patients [1,5,6]. Uncertainty about the chance of successful extubation can further delay weaning from ventilation [7–9].

Neurocritical care patients often include a wide age range compared to other critically ill patients, as various types of brain injuries can affect different age groups [10]. While trauma is a more common cause of brain injury in younger patients, in older patients, brain injury is frequently associated with cerebrovascular diseases or the use of systemic anticoagulants. These underlying causes may influence overall outcomes. Furthermore, aging affects the respiratory system by reducing chest wall compliance due to structural changes and increasing lung compliance from decreasing elastic recoil [11], causing 'senile emphysema' due to loss of supportive structures [12,13] and results in a decline in respiratory muscle strength, impairing effective cough [14–17]. These changes begin at the age of 20 to 25 years and are ongoing [18], potentially affecting ventilation outcomes as well [19].

We conducted a posthoc analysis of a large worldwide observational study focused on the epidemiology and outcomes of intubated and ventilated neurocritical care patients- the ENIO study [20]. The aim of this analysis was to examine associations of age with extubation failure, the primary endpoint of the original study. We hypothesized that age has an independent association with extubation failure. To test this hypothesis, we performed an unadjusted analysis and an adjusted analysis wherein we used logistic regression models to control for observed confounding factors that might influence the primary outcome.

2. Methods

2.1. Study design

This is a posthoc analysis of 'Extubation strategies in Neuro–Intensive care unit patients and associations with Outcomes study' (ENIO). ENIO was an international, prospective observational study, conducted in 73 ICUs in 18 countries from 2018 to 2020. Initial approval was obtained from Groupe Nantais d'Éthique dans le Domaine de la Santé, Nantes, France (No. 7-11-2017) and prepublished [21]. The protocol of ENIO was approved by the local institutional review boards in accordance with local regulations. Given the observational nature of ENIO, individual patient consent was waived, except for centers in countries where informed consent was obligatory due to local regulations.

2.2. Patients

Patients were eligible for participation in ENIO if they met the following criteria: [1] admitted for a neurocritical disorder with a Glasgow Coma Scale score ≤ 12; [2] receiving invasive ventilation for at least 24 h; and [3] undergoing an attempt to be liberated from the ventilator.

Patients were excluded if < aged 18 years, pregnant patients, patients with spinal cord injury above T4, patients after cardiac arrest, and patients with Guillain–Barré syndrome, motor neuron disease, muscular dystrophy or myasthenia gravis were also excluded. Death before extubation, withdrawal of life–sustaining treatment (WLST) in the first 24 h after ICU admission, end–of–life extubation, major respiratory comorbidities and major chest trauma were additional reasons for exclusion.

All patients included in ENIO were eligible for participation in this posthoc analysis. However, patients undergoing WLST after the first 24 h were additionally excluded.

2.3. Data collected

ENIO captured data from June 2018 to November 2020. The following demographic and baseline data were collected: age, gender, body height and weight, type and location of brain injury, baseline Glasgow Coma Scale score, and data on initial neurocritical care management. Data on ventilation management, including ventilation mode, tidal volume (V_T), positive end–expiratory pressure (PEEP), respiratory rate (RR), plateau pressure (Pplat) and fraction of inspired oxygen (FiO_2), arterial blood gas analyses results, including pH, partial arterial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide (PCO_2), sedation management, and use of neuro muscular blocking agents other than used for intubation, was collected at day 1, day 3 and day 7 in the ICU. In addition, it was recorded whether a patient developed pneumonia or ARDS as defined by the Berlin criteria, during their entire ICU stay. The date of the first successful spontaneous breathing trial (SBT), the first extubation attempt, and if it happened, placement of tracheostoma was recorded. On the day of the first extubation, data on general management, such as the use of corticosteroids, to prevent post–extubation stridor, and enteral nutrition discontinuation, was also collected.

Follow–up consisted of the following: any re–intubation up to day 28, discharge from the ICU to the general ward, discharge from the hospital, and mortality until the last day in hospital.

2.4. Definitions and calculations

We defined 'extubation failure' as outlined in the analysis plan of the ENIO study, as the need for reintubation following the first planned or accidental extubation attempt. All patients were monitored from extubation until ICU discharge. For patients with an ICU stay exceeding 28 days, monitoring for reintubation ceased after 28 days. Duration of mechanical ventilation was defined as the time between start of invasive ventilation and date of extubation. Length of stay was defined as the time between ICU admission and ICU discharge. All–cause ICU– and hospital mortality included death in ICU and hospital, respectively.

V_T is expressed in ml/kg predicted body weight (PBW), using the formulas for males and females [22]. Driving pressure (ΔP) [23], respiratory system compliance (C_{RS}) [24], and mechanical power of ventilation (MP) [25] were calculated during controlled ventilation.

2.5. Primary and secondary endpoints

The primary endpoint of this analysis was extubation failure by day 5. This endpoint was chosen since it was the primary endpoint of ENIO—90 % of extubation failure occurred within 5 days after extubation. Secondary endpoints included duration of ventilation, length of stay in ICU and hospital, and all–cause ICU and hospital mortality.

2.6. Sample size calculation

We did not perform a formal power calculation—instead, the number of patients available in the database was used as the sample size.

2.7. Statistical analysis

Descriptive statistics were used to describe patient demographics and baseline characteristics, and ventilator settings and ventilation parameters. Continuous variables are expressed in medians and interquartile ranges, categorical variables are expressed in frequencies and proportions.

Patients were categorized into four age groups based on age quartiles. Baseline characteristics and ventilation settings and parameters at day 1 of the age groups were compared using the Kruskal–Wallis test for continuous variables and chi-squared test for categorical variables.

Key ventilator settings and ventilation parameters, including V_T, PEEP, FiO_2, RR, ΔP and MP for the four age groups are presented in cumulative distribution plots and line graphs. Trends over time are assessed with mixed-effect linear models with patients treated as random effect to account for clustering and repeated measurements, and with day, age group and their interaction as fixed effect. *P* values from this analysis represent the overall difference among age groups over time and P values from interaction represents the difference in trend over time among the age groups.

Time–to–event outcomes were presented in Kaplan–Meier curves. Logistic regression was used to study the differences of the binary clinical outcomes, including 5-day extubation failure, in ICU and in hospital mortality per age group with the youngest group as reference group, presented as odds ratios (OR) and 95 % confidence intervals (CIs). Cox proportional hazard modelling was used to assess the differences of the continuous clinical outcomes, including duration of ventilation and duration of ICU stay, per age groups with the youngest group as reference group, presented as hazard ratios (HR) and 95 % CIs.

To further assess the association of age as a continuous variable with the primary endpoint, extubation failure by day 5, we used multivariate logistic regression and adjusted for unequal distribution of effect modifiers, presented as OR and 95 %–CIs. We adjusted for baseline covariates selected according to clinical relevance and as used in previous studies [26,27], including: gender, body mass index (BMI), Glasgow Coma Scale score at admission, PaO_2 to FiO_2 ratio and type of brain injury. We also adjusted for the earlier identified and published risk factors for extubation failure [20], including (i.) chronic hypertension at baseline, posterior fossa injury, neurosurgery, plateau pressure and pH and (ii.) at day of extubation; Glasgow Coma Scale—eyes score, Glasgow Coma Scale—motor score, heart rate, respiratory rate, temperature, duration of positive pressure, presence of endotracheal suctioning ($\leq$ 2 times/h), cough (moderate or vigorous), swallowing attempt, visual pursuit and gag reflex. To assess potential multicollinearity among the covariates included in the multivariate analyses, we calculated the variance inflation factor (VIF) for each variable. The VIF value of each variable was below 5, indicating low correlation and an acceptable level of multicollinearity. In the adjusted analysis, we checked the validity of the linearity assumption of the logistic model and confirmed that the assumption held true.

In one posthoc analysis, we tested the prognostic capacity of the 'successful extubation prediction score' as developed in the primary analysis of ENIO [20], across the four age groups. Multiple imputation by chained equations (MICE) was performed in the setting of missing data. The performance of the score was evaluated using receiver operating characteristic (ROC) curves. The area under the ROC (AUC) was calculated for each group, and compared using the DeLong test [28]. Sensitivity, specificity, and positive and negative predictive values were calculated for all four age groups, using the threshold of 70, as previously established in the primary analysis of ENIO [20].

Data were analyzed with R (R Core Team, 2022, Vienna, Austria, version 4.2.2). Statistical uncertainty was expressed by 95 % confidence levels. A *P* value $<$0.05 was considered statistically significant.

3. Results

3.1. Patients

A total of 1095 patients in 73 centers in 18 countries from 2018 to 2020 were included in this analysis (Fig. 1). Median age was 53 [35 to 65] years The types of brain injury varied across age groups (Table 1). Younger patients were more likely to be admitted with traumatic brain injury, while older patients more often had cerebral hemorrhage, ischemic stroke, central nervous infection, or brain malignancies. Therapeutic hypothermia, barbiturate coma and decompressive

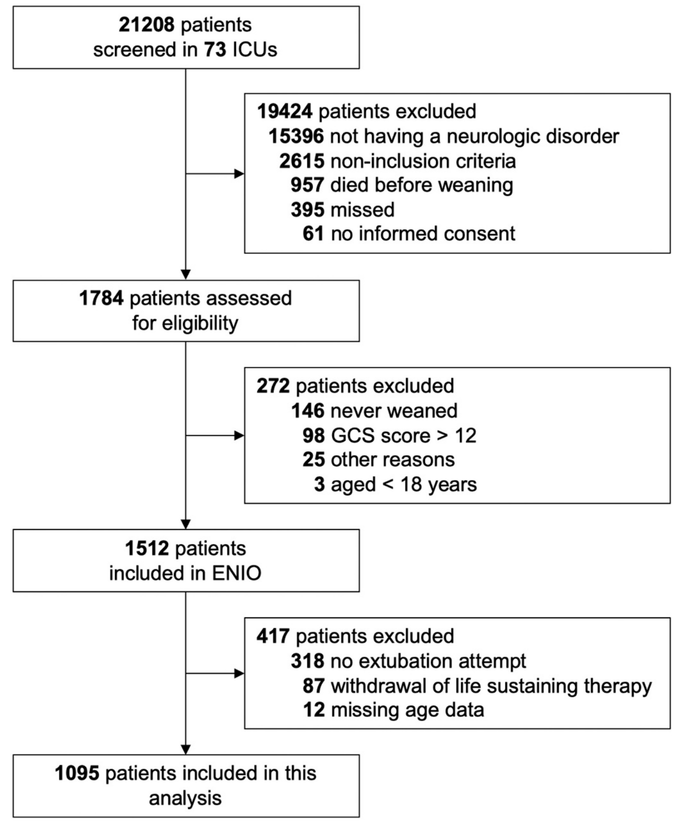

Fig. 1. CONSORT diagram. Flow of patients in ENIO, and in this analysis.

craniectomy were more often used in younger patients, external ventricular drains were more frequently placed in older patients. Older patients tended to be shorter and were more often diagnosed with comorbidities, including pulmonary disease, heart failure, hypertension, diabetes and malignancies, whereas younger patients were more often active smokers. Key ventilator settings and ventilation parameters were not meaningful different across age groups (Table 2, Fig. 2, and **Online Supplement eFigure 1**).

3.2. Extubation failure

The primary endpoint, extubation failure by day 5, occurred in 209 (19 %) patients (**Online Supplement eFigure 2)**. In the unadjusted analysis, older patients had a higher risk of extubation failure (odds ratio (OR) for each one–year increase in age, 1.012 [95 % confidence interval 1.004 to 1.021]; $P = 0.006$). However, after adjusting for confounders, the association was no longer statistically significant (OR 1.008, 95 % confidence interval 0.997–1.019; $P = 0.172$). All variables used in the adjusted model are shown in Online Supplement eTable 2.

3.3. Other endpoints

Age had no association with duration of ventilation, ICU length of stay, or ICU mortality but was associated with higher hospital mortality (Table 3).

3.4. Posthoc analysis

The prognostic performance of the 'successful extubation prediction score' was consistent across the four age groups when using the threshold applied in the confirmation cohort in the original ENIO analysis (**Online Supplement eFigure 3** and **eTable 2**).

Table 1
Baseline Demographics and Patient Characteristics.

	Age ≥ 18 and < 36 years (N = 278)	Age ≥ 36 and ≤ 53 years (N = 281)	Age ≥ 54 and ≤ 65 years (N = 275)	Age > 65 years (N = 261)	P–value
Age (years), median [IQR]	26 [22 to 29]	46 [41 to 51]	60 [56 to 63]	72 [69 to 76]	<0.001
Male, n (%)	228 (82)	202 (72)	162 (59)	156 (60)	<0.001
Weight (kg), median [IQR]	70 [62 to 80]	77 [66 to 89]	78 [67 to 90]	76 [67 to 85]	<0.001
Height (cm), median [IQR]	172 [166 to 180]	173 [165 to 180]	170 [164 to 175]	170 [162 to 175]	<0.001
BMI (kg/m^2), median [IQR]	24 [22 to 26]	25 [23 to 29]	27 [24 to 30]	26 [23 to 29]	<0.001
Comorbidities					
Pulmonary disease, n (%)	0 (0)	3 (1)	18 (7)	16 (6)	<0.001
Heart failure, n (%)	0 (0)	3 (1)	13 (5)	17 (7)	<0.001
Hypertension, n (%)	2 (1)	49 (17)	118 (43)	147 (56)	<0.001
Active smoking, n (%)	58 (21)	81 (29)	63 (23)	37 (14)	<0.001
Diabetes, n (%)	2 (1)	81 (29)	43 (17)	64 (25)	<0.001
Malignancy, n (%)	4 (1)	10 (4)	11 (4)	25 (10)	<0.001
Type of brain injury					
Traumatic brain injury, n (%)	236 (85)	131 (47)	84 (31)	97 (37)	<0.001
Hemorrhage, n (%)	16 (6)	100 (36)	130 (47)	97 (37)	<0.001
Ischemic stroke, n (%)	8 (3)	22 (8)	29 (11)	33 (13)	<0.001
Central nervous infection, n (%)	8 (3)	12 (4)	11 (4)	13 (5)	0.66
Brain tumor, n (%)	7 (3)	13 (4)	14 (5)	17 (6)	0.17
Other, n (%)	3 (1)	3 (1)	7 (3)	4 (2)	0.50
GCS scores					
GCS at baseline, median [IQR]	7 [5 to 8]	7 [5 to 9]	7 [4 to 9]	7 [6 to 9]	0.36
Neurocritical management					
Intracranial probe, n (%)	129 (46)	126 (45)	147 (53)	104 (40)	0.02
External ventricular drainage, n (%)	40 (14)	78 (28)	112 (41)	86 (33)	<0.001
Therapeutic hypothermia, n (%)	15 (5)	9 (3)	19 (7)	4 (2)	0.01
Barbiturate coma, n (%)	29 (10)	16 (6)	6 (2)	6 (2)	<0.001
Neurosurgery, n (%)	98 (35)	118 (42)	95 (35)	100 (38)	0.25
Decompressive craniectomy, n (%)	67 (24)	51 (18)	36 (13)	23 (9)	<0.001
ICU events					
Health care–related pneumonia, n (%)	97 (35)	103 (37)	123 (45)	91 (35)	0.05
ARDS, n (%)	30 (11)	17 (6)	30 (11)	18 (7)	0.08

Data presented as median with interquartile range [25th to 75th quartile] or n (%). Abbreviations: ARDS, Acute Respiratory Distress Syndrome; BMI, Body Mass Index; and GCS, Glasgow Coma Scale.

4. Discussion

The findings of this posthoc analysis of an international, prospective observational study, conducted in 73 ICUs in 18 countries from 2018 to 2020, can be summarized as follows: (i.) in the unadjusted analysis, age was found to be associated with extubation failure; however, (ii.) after adjusting for baseline covariates and previously identified risk factors for extubation failure, age was not significantly associated with extubation failure. Additionally, (iii.) there was no association between age and duration of ventilation, ICU length of stay, or ICU mortality. However, (iv) age was associated with an increased risk of hospital mortality.

Our study has several strengths. We included a large and diverse patient population from multiple types of centers across various countries and continents, which enhances the generalizability of our findings. The data were collected prospectively, ensuring a high level of accuracy and reliability, with minimal missing data and nearly complete follow–up. The broad age range of neurocritical patients in our cohort, due to the varying types of brain injuries across age groups, allowed for a comprehensive assessment of age–related associations with the clinical outcome. Age groups were sufficiently represented, enabling meaningful comparisons across categories. To assess the impact of age on our primary outcome, extubation failure by day 5, we analyzed age both as quartiles and as a continuous variable. Using quartiles allowed for a balanced presentation of baseline characteristics, while treating age as a continuous variable in the multivariate logistic regression model provided a more nuanced evaluation. This dual approach ensures both data–based and clinically relevant perspectives are considered in understanding the relationship between age and extubation failure. Furthermore, our analysis was rigorous, adjusting not only for baseline covariates but also for previously identified risk factors for extubation failure.

Our findings indicate that age may not be regarded as a relevant factor in decision–making for extubation in brain injured patients. This is an interesting finding since elderly patients with brain injury are generally regarded as more vulnerable and having worse outcomes than younger patients. Other observational studies across different cohorts of ICU patients, including neurocritical care patients, have found an association with age and extubation failure [29–37]. Unlike previous studies, we adjusted not only for baseline covariates but also for known risk factors for extubation failure [20], demonstrating that age does not independently predict extubation outcomes when other covariates are controlled for. It may be that frailty, rather than age, is associated with extubation outcomes. Recent studies have shown that frailty in general ICU patients is associated with increased risk on extubation failure and prolonged mechanical ventilation [38]. Unfortunately, frailty was not captured in ENIO.

We found that age was not associated with duration of ventilation, ICU length of stay, or ICU mortality, likely because these outcomes are also more closely linked to frailty. A recent study in neurocritical care patients showed that higher frailty scores, regardless of age, were associated with worse outcomes [39]. Our finding that age was associated with higher hospital mortality aligns with findings in previous studies in both general ICU population [40–43] and neurocritical care cohorts [10,44], where older age has been identified as a risk factor for mortality. However, the evidence regarding the association between age and the duration of ventilation and ICU stay remains less clear [45–51].

Our study reports an extubation failure rate that is nearly double that observed in the general ICU population [29,30,33–36,52] and four times as high as the rate seen in post–cardiac surgery patients [31,32]. However, the rate we found aligns with or is even lower than those reported in other cohorts of neurocritical care patients, as recently found in one meta–analysis [37]. The elevated rates of extubation failure in

Table 2
Ventilation Settings, Variables and Parameters on Day of Admission

	Age ≥ 18 and < 36 years (N = 278)	Age ≥ 36 and ≤ 53 years (N = 281)	Age ≥ 54 and ≤ 65 years (N = 275)	Age > 65 years (N = 261)	P–value
Mode of ventilation					
Pressure assist/control, n (%)	71 (26)	91 (33)	65 (24)	80 (31)	<0.001
Volume assist, n (%)	199 (72)	184 (66)	202 (75)	169 (66)	<0.001
Spontaneous breathing, n (%)	6 (2)	4 (1)	3 (1)	8 (3)	<0.001
Ventilatory variables					
V_T (ml/kg PBW), median [IQR]	7 [6 to 7]	7 [6 to 8]	7 [7 to 8]	7 [7 to 8]	<0.001
PEEP (cm H_2O), median [IQR]	5 [5 to 6]	5 [5 to 6]	5 [5 to 6]	5 [5 to 6]	0.10
RR (breath/min), median [IQR]	16 [15 to 20]	17 [15 to 20]	17 [15 to 20]	16 [15 to 20]	0.33
Pplat (cmH_2O), median [IQR]	16 [14 to 18]	16 [13 to 19]	16 [13 to 19]	15 [14 to 18]	0.45
PaO_2 (mmHg), median [IQR]	120 [99 to 171]	120 [90 to 163]	109 [84 to 137]	106 [87 to 141]	<0.001
PCO_2 (mmHg), median [IQR]	37 [34 to 41]	38 [34 to 41]	37 [35 to 41]	37 [34 to 42]	0.74
FiO_2 (%), median [IQR]	40 [30 to 50]	40 [30 to 50]	40 [30 to 50]	40 [30 to 50]	0.73
pH, median [IQR]	7.4 [7.3 to 7.4]	7.4 [7.3 to 7.4]	7.4 [7.4 to 7.4]	7.4 [7.4 to 7.4]	0.003
Static C_{rs}, median [IQR]	44 [34 to 58]	46 [36 to 60]	44 [34 to 60]	47 [38 to 58]	0.31
ΔP (cmH_2O), median [IQR]	10 [8 to 13]	10 [8 to 13]	10 [8 to 13]	10 [8 to 12]	0.37
MP (J/min), median [IQR]	7 [6 to 9]	8 [6 to 10]	8 [7 to 10]	7 [6 to 9]	0.01
Sedation and analgesia management					
Midazolam, n (%)	191 (69)	169 (60)	142 (52)	98 (38)	<0.001
Propofol, n (%)	194 (70)	198 (70)	186 (68)	170 (65)	0.39
Dexmedetomidine, n (%)	52 (19)	32 (11)	13 (5)	20 (8)	<0.001
Pentothal, n (%)	17 (6)	12 (4)	6 (2)	5 (2)	0.07
Neuromuscular blocking agents, n (%)	33 (12)	25 (9)	32 (12)	15 (6)	0.21
Management of extubation					
Cuff leak test performance, n (%)	140 (50)	113 (40)	90 (33)	74 (28)	<0.001
Use of corticosteroids, n (%)	84 (30)	59 (21)	53 (19)	41 (16)	<0.001
Discontinuation of enteral nutrition, n (%)	185 (67)	171 (61)	183 (67)	153 (59)	0.09
Reason for extubation failure					
Neurological impairment, n (%)	10 (26)	22 (37)	29 (42)	30 (50)	0.12
Respiratory failure, n (%)	24 (63)	32 (54)	39 (57)	28 (47)	0.43
Airway failure, n (%)	14 (37)	19 (32)	25 (36)	23 (38)	0.91
Cardiac failure, n (%)	0 (0)	1 (2)	0 (0)	3 (5)	0.14
Surgery, n (%)	4 (11)	7 (12)	7 (10)	4 (7)	0.80
Other, n (%)	1 (3)	3 (5)	1 (1)	3 (5)	0.62

Data presented as median with interquartile range [25th to 75th quartile] or n (%). Abbreviations: ΔP, driving pressure; FiO_2, fraction of inspired oxygen; MP, mechanical power; PaO_2, partial arterial oxygen pressure; PCO_2, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; C_{rs}, respiratory system compliance; RR, respiratory rate; and V_T, tidal volume.

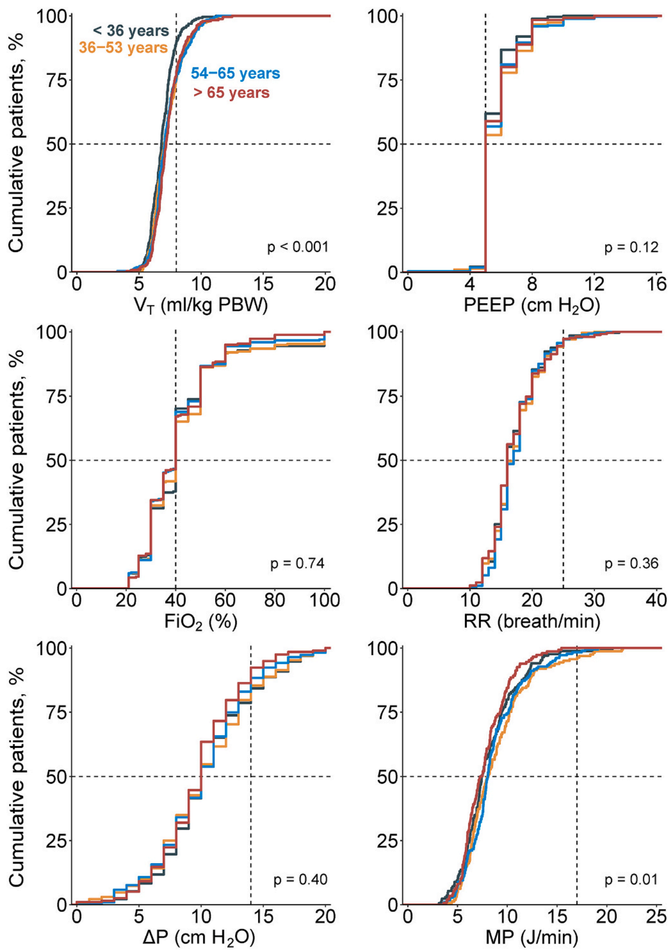

Fig. 2. Cumulative frequency distribution plots of key ventilator settings and ventilation parameters for the age groups based on age quartiles at day 1. Horizontal dotted lines represent the median for each variable, and vertical dotted lines represent the ideal cutoff for each parameter.
Abbreviations: V_T, tidal volume; PEEP, positive end–expiratory pressure; FiO_2, fraction of inspired oxygen; RR, respiratory rate; ΔP, driving pressure; and MP, mechanical power of ventilation.

Table 3
Association of Age Category with Clinical Outcomes.

		OR/HR*	95 %–CI*	P–value*
5-day extubation failure	**n (%)**			
Age ≥ 18 and < 36 years**	35 (13)			
Age ≥ 36 and ≤ 53 years	57 (20)	1.77	1.12–2.81	0.01
Age ≥ 54 and ≤ 65 years	59 (21)	1.90	1.21–3.02	0.01
Age > 65 years	58 (22)	1.98	1.26–3.16	0.003
Duration of ventilation	**Median [IQR]**			
Total				
Age ≥ 18 and < 36 years**	7 [4 to 12]			
Age ≥ 36 and ≤ 53 years	7 [3 to 11]	1.04	0.88–1.24	0.61
Age ≥ 54 and ≤ 65 years	8 [4 to 16]	0.81	0.69–0.97	0.02
Age > 65 years	6 [2 to 13]	1.01	0.85–1.20	0.89
Duration of ventilation	**Median [IQR]**			
Before first extubation attempt				
Age ≥ 18 and < 36 years**	6 [3 to 12]			
Age ≥ 36 and ≤ 53 years	7 [3 to 10]	1.09	0.92–1.29	0.30
Age ≥ 54 and ≤ 65 years	7 [3 to 13]	0.95	0.80–1.13	0.56
Age > 65 years	5 [2 to 10]	1.11	0.93–1.31	0.24
Duration of ventilation	**Median [IQR]**			
*After reintubation****				
Age ≥ 18 and < 36 years**	4 [2 to 7]			
Age ≥ 36 and ≤ 53 years	5 [0 to 10]	0.84	0.54–1.29	0.43
Age ≥ 54 and ≤ 65 years	7 [3 to 14]	0.55	0.36–0.85	0.007
Age > 65 years	6 [3 to 13]	0.59	0.38–0.92	0.02
Duration of ICU stay	**Median [IQR]**			
Age ≥ 18 and < 36 years**	11 [7 to 18]			
Age ≥ 36 and ≤ 53 years	13 [7 to 20]	0.92	0.78–1.09	0.33
Age ≥ 54 and ≤ 65 years	15 [9 to 27]	0.73	0.61–0.86	<0.001
Age > 65 years	11 [6 to 23]	0.91	0.76–1.07	0.26
ICU mortality	**n (%)**			
Age ≥ 18 and < 36 years**	1 (0)			
Age ≥ 36 and ≤ 53 years	1 (0)	0.99	0.04–25.19	1.00
Age ≥ 54 and ≤ 65 years	7 (3)	7.24	1.28–135.73	0.07
Age > 65 years	6 (2)	6.49	1.10–123.09	0.08
Hospital mortality	**n (%)**			
Age ≥ 18 and < 36 years**	4 (1)			
Age ≥ 36 and ≤ 53 years	5 (2)	1.27	0.33–5.17	0.73
Age ≥ 54 and ≤ 65 years	16 (6)	4.22	1.52–14.87	0.01
Age > 65 years	29 (11)	8.61	3.33–29.36	<0.001

Data presented as median with interquartile range [25th to 75th quartile] or n (%).
* OR, Odds Ratio; HR, Hazard Ratio; 95 %–CI, 95 %–confidence interval; and *P*-value using logistic regression (binary outcomes) or cox proportional hazard model (continuous outcomes).
** Reference group.
*** This includes only patients who were reintubated.

neurocritical care patients may result from factors such as impaired consciousness, which complicates safe extubation and increases the aspiration risk with higher incidences of ventilator–associated pneumonia [53]. Evidence to guide extubation in this population remains limited [7,9], and standard weaning criteria may not be appropriate [54], resulting in significant variation in practice across different settings and countries and centers [55].

The 'successful extubation prediction score' demonstrated consistent performance across all four age groups when applying the threshold used in the confirmation cohort in the original ENIO analysis [20]. This finding underlines the robustness of the score and suggest that it can be reliably applied regardless of a patient's age.

Our analysis has several limitations. Since ENIO was an observational study, we can only infer associations, not causality, between age and outcomes. Awareness of the study's data collection may have influenced extubation practices. While the broad participating of centers helps to minimize selection bias, certain confounding factors related to patient conditions or clinical features may still be unaccounted for. Extubation failure, as outlined in the analysis plan of the ENIO study, was defined strictly as to the need for reintubation, and did not account for the use of noninvasive ventilation (NIV), high–flow nasal oxygen (HFNO), or tracheostomy. This definition may be considered a limitation, as it does not account for these alternative forms of respiratory support, which could represent clinically significant forms of extubation failure. Future studies should capture this data. Follow–up in ENIO was restricted to the hospital stay, constraining our horizon to short–term outcomes and excluding long–term outcomes, functional outcomes and quality of life. This constraint affects our ability to fully evaluate the impact of age on overall neurocritical care outcomes. Additionally, the absence of data on the causes of death in the ENIO database restricts the ability to examine how withdrawal of life sustaining treatment affects outcomes. Future studies should collect this information, as it could provide valuable insights into the role of withdrawal of life sustaining treatment, particularly since it may be more frequently applied in certain patient groups like older patients.

5. Conclusion

In this large international cohort of invasively ventilated neurocritical care patients with various types of brain injuries, age was found to have no association with extubation failure after adjusting for baseline covariates and previously identified risk factors. Therefore, age may not be a relevant factor to consider in extubation decisions for brain–injured patients. Consistent with this finding, the 'successful extubation prediction score' demonstrated reliable performance across all four age groups. This underlines the robustness of the score and suggest that it can be effectively applied regardless of a patient's age.

CRediT authorship contribution statement

Relin van Vliet: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **David M.P. van Meenen:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Chiara Robba:** Writing – review & editing, Investigation. **Raphaël Cinotti:** Writing – review & editing, Investigation. **Karim Asehnoune:** Writing – review & editing, Investigation. **Robert D. Stevens:** Writing – review & editing, Investigation. **Denise Battaglini:** Writing – review & editing, Investigation. **Shaurya Taran:** Writing – review & editing, Investigation. **Mathieu van der Jagt:** Writing – review & editing, Investigation. **Fabio Silvio Taccone:** Writing – review & editing, Investigation. **Frederique Paulus:** Writing – review & editing, Methodology, Conceptualization. **Marcus J. Schultz:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Chiara Robba:** Writing – review & editing, Investigation. **Denise Battaglini:** Writing – review & editing, Investigation. **Mathieu van der Jagt:** Writing – review & editing, Investigation. **David Michael Paul van Meenen:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Marcus J. Schultz:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Robert David Stevens:** Writing – review & editing, Investigation.

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Declaration of competing interest

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

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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.2025.155067.

Data availability

A deidentified dataset will be made available upon request to the corresponding author at least 1 year after the publication of this study. The request must include a statistical analysis plan.

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