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ORIGINAL

Ventilation practices in acute brain injured patients and association with outcomes: the VENTIBRAIN multicenter observational study

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Abstract

Purpose: Current mechanical ventilation practices for patients with acute brain injury (ABI) are poorly defined. This study aimed to describe ventilator settings/parameters used in intensive care units (ICUs) and evaluate their association with clinical outcomes in these patients.

Methods: An international, prospective, multicenter, observational study was conducted across 74 ICUs in 26 countries, including adult patients with ABI (e.g., traumatic brain injury, intracranial hemorrhage, subarachnoid hemorrhage, and acute ischemic stroke), who required ICU admission and invasive mechanical ventilation. Ventilatory settings were recorded daily during the first week and on days 10 and 14. ICU and 6-months mortality and 6-months neurological outcome were evaluated.

Results: On admission, 2095 recruited patients (median age 58 [interquartile range 45–70] years, 66.1% male) had a median plateau pressure (Pplat) of 15 (13–18) cmH_20, tidal volume/predicted body weight 6.5 (5.7–7.3) mL/Kg, driving pressure 9 (7–12) cmH_20, and positive end-expiratory pressure 5 (5–8) cmH_20, with no modifications in case of increased intracranial pressure (> 20 mmHg). Significant differences in practices were observed across different countries. The majority of these ventilatory settings were associated with ICU mortality, with the highest hazard ratio (HR) for Pplat (odds ratio 1.50; 95% confidence interval, CI: 1.27–1.78). The results demonstrated consistent association with 6-month mortality; less clear association was observed for neurological outcome.

Conclusions: Protective ventilation strategies are commonly used in ABI patients but with high variability across different countries. Ventilator settings during ICU stay were associated with an increased risk of ICU and 6-month mortality, but not an unfavorable neurological outcome.

Keywords: Mechanical ventilation, Acute brain injury, Traumatic brain injury, Cerebrovascular disease, Outcome

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Introduction

Mechanical ventilation (MV) is a fundamental component of the intensive care unit (ICU) management of acute brain injured (ABI) patients [1–3]. Over the last decades, lung protective strategies (LPS) have become the standard of care after demonstrating to improve clinical outcomes [4, 5] in mechanically ventilated ICU patients, regardless of the diagnosis of acute respiratory distress syndrome (ARDS) [6]. However, clinical trials establishing the effect of LPS often excluded ABI patients from enrollment, due to their potentially detrimental effects on cerebral physiology [4, 5]. In particular, the need for low plateau pressure (Pplat) and low tidal volumes (TV), with consequent hypercapnia and increased intracerebral blood volume could be challenging in ABI patients at high risk of intracranial hypertension [7–10]. Moreover, high positive end-expiratory pressures (PEEP), resulting in increased intrathoracic pressure and reduced cerebral venous outflow, could favor hemodynamic instability, reduce cerebral perfusion pressure and increase intracranial pressure (ICP) [7–9, 11].

As such, strong evidence on the best ventilatory strategies to be applied in the ABI populations is lacking. Only a post hoc analysis [12] of an observational cohort suggested that the use of LPS has increased in this population over the last decade, but there are no specific studies primarily focusing on the ABI population [13]. Consequently, the most recent guidelines on MV in ABI patients from the European Society of Intensive Care Medicine [14] are based on a very low level of evidence and/or expert opinion and highlight the need for specific research in this field.

We, therefore, conducted the prospective, multicenter observational VENTIBRAIN study [15] to describe the current practice of MV in ABI patients and assess its association with clinical outcomes. We hypothesize that the use of lung protective strategies is frequently applied in ABI patients and that these have an association with clinical outcomes.

Take-home messages

Ventilator settings in acute brain injury (ABI) patients significantly vary across countries, and while protective strategies are commonly used, they are inconsistently applied. Plateau pressure is strongly associated with increased intensive care unit (ICU) and 6-month mortality, emphasizing the importance of tailored ventilation strategies. The association between ventilator settings and mortality highlights the need for further research and standardized guidelines to optimize care for ABI patients in the ICU

Methods

Study design and participants

This was a prospective, multicenter, observational cohort study conducted at 74 ICUs in 26 countries (electronic supplementary material figure 2) from November 25th, 2020, to October 15th, 2023. The inclusion criteria were adult (> 18 years) patients admitted to ICU with a diagnosis of a primary non-anoxic ABI, e.g., traumatic brain injury (TBI), intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH) or acute ischemic stroke (AIS), and requiring intubation and MV. Patients were excluded if pregnant (confirmed or suspected) or if they received only non-invasive ventilation. The full study protocol was previously published [15]. This study was conducted according to the STROBE guidelines (electronic supplementary material 2, item 1), was registered at ClinicalTrial.gov (NCT04459884), and was endorsed by the European Society of Intensive Care Medicine (ESICM) (https://www.esicm.org/endorsed-trials/ongoing-projects-endorsed/).

Ethical approval was obtained from the University of Milano-Bicocca by the ethics committee Brianza ASST-Monza on 10/09/2020 (Approval number 3425, amendment on 25/02/2021), and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Since patients included in the study were intubated and could not provide informed consent at the time of study recruitment, each center referred to local or national law on the issue of inability to provide consent. If patients regained consciousness and the ability to provide consent at the follow-up visit, they were required to confirm the initial consent for the use of data. National or local approvals at study sites were obtained by national coordinators and local principal investigators, according to local regulations.

Study objectives and definitions

The primary objective of the study was to describe the ventilatory settings/parameters applied in mechanically ventilated ABI patients admitted to the ICU. Secondary aims included: description of ventilatory settings/parameter in the presence/absence of intracranial hypertension (ICP > 20 mmHg [16, 17]); assess the heterogeneity in ventilatory settings among countries; describe their association with ICU, 6-month mortality and 6-month functional neurologic outcome.

An unfavorable neurological outcome was defined as an extended Glasgow Outcome Scale (GOSE) < 5 [18]. Outcomes at 6 months were collected via phone with structured interviews with the patients and/or family members [18]. Countries were categorized according to their Gross National Income (GNI) per capita into high-income, upper middle income and lower middle income as defined using the Atlas Method (www.worldbank.or). LPS was defined as TV/predicted body weight (PBW) ≤ 8 m L/Kg and Pplat ≤ 30 cmH20 [19].

Procedures and data collection

Pseudo-anonymized data were collected in a web-based electronic case report form (eCRF) and protected by encryption software and passwords provided to single users. The data were securely stored at the University Milano-Bicocca. All procedures complied with the EU Regulation 2016/679 on the protection of natural persons regarding personal data processing and movement. A data transfer agreement to confirm the terms for data transfer from the centers to the sponsor was finalized.

Data were collected on admission, daily until day 7 from ICU admission and at days 10 and 14: demographics, neurological clinical status (i.e., pupils' characteristics and Glasgow Coma Scale, GCS), neuroradiological scores, type of neuromonitoring, therapy intensity levels for intracranial hypertension management [20], vital parameters, and the occurrence of neurological and systemic complications (such as pneumonia-community and hospital-acquired pneumonia, ventilator-associated pneumonia (according to the Clinical Pulmonary Infection Score), pneumothorax, and ARDS (according to the Berlin definition [21])). ICP data were obtained at 8 a.m. (first record in the morning); the lowest and highest ICP values during the day were also noted. Ventilator settings included mode of ventilation, tidal volume (TV), TV/PBW, Pplat, peak pressure (Ppeak), PEEP, respiratory rate (RR) and inspired fraction of oxygen (FiO_2), and were obtained at 8 a.m. Further ventilatory parameters from arterial blood gas (including Ph and partial pressure of oxygen/carbon dioxide) were collected. Driving pressure (safe value < 15 cmH_20) was calculated as the difference between Pplat-PEEP and mechanical power according to previously validated formulas [22–24]. Static compliance was calculated as tidal volume/driving pressure.

Statistical analysis

Continuous variables were described by median and 25th and 75th percentiles, while categorical variables by absolute and relative frequencies. Linear mixed-effects models were used to assess the heterogeneity between countries of every ventilator setting/parameter measured over time, with individual and country as random intercepts effects and age, sex, type of brain injury, GCS motor score, baseline PaO_2/FiO_2 ratio and pupillary reactivity as fixed effects [25]. We quantified the country-level variance partition coefficient (VPC) and the intraclass correlation coefficient (ICC). The first describes the amount of the total variability of every ventilator setting/parameter due to differences among countries, and the latter represents the correlation among ventilation setting/parameter in patients within the same countries. High values of country-level ICC (i.e., close to one) indicate high homogeneity among patients within the same country, while lower values (i.e., close to zero) suggest a lower country contextual effect.

The 6-month crude mortality was estimated by Kaplan–Meier. The association between every ventilator setting/parameter and ICU and 6-month mortality was investigated using the time-dependent Cox proportional regression hazard models with the same adjustments above (except for baseline PaO_2/FiO) [26]. The functional form of the relation between continuous predictors (i.e., age and ventilator/setting parameters) and the outcome was investigated using three-knot restricted cubic splines. The linear/non-linear form was established based on the lowest Akaike Information Criterion (AIC) [27]. The relation between the ventilator settings/parameters and mortality was visually shown through the log relative hazard of ICU mortality for every parameter. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were estimated and provided for the 75th versus 25th percentile. The 6-month unfavorable neurological outcome (GOSE score < 5) was also investigated based on the same modeling approach, but using the regression logistic models, but summarizing the longitudinal profile of the ventilation setting/parameters with their mean. These regression models were performed first by considering the contribution of each ventilator setting/parameter alone and subsequently by considering all together the ventilator settings and parameters, respectively. Results of the latter models were reported with odds ratios (OR) and the corresponding 95% CIs. All analyses were performed using R software version 4.32.3 [28].

Results

Patients' characteristics

A total of 2136 patients were consecutively screened and 2095 were included in the analysis (52.8% of the patients were from Europe, 28.8% from Asia, 12.2% from the Americas and 6.2% from Africa—electronic supplementary figures 1-2). Baseline characteristics are reported in Table 1. The median age was 58 (interquartile range (IQR) 45–70) years, 1384 (66.1%) were male and 1294 (61.8%) were from high-income countries. Overall, 837 (40%) patients were admitted for TBI, 568 (27.1%) for ICH, 402 (19.2%) for SAH and 288 (13.7%) for AIS. Median GCS on admission was 7 (4–10). ARDS occurred in 478 patients (14.8% mild, 8.8% moderate, 1.1% severe) (electronic supplementary table 1).

Table 1 Baseline characteristics and ventilatory settings

	Total ($N = 2095$)
Baseline characteristics	
Median age, *years* (*n* = 2094)	58 (45, 70)
Sex (*n* = 2095)	
Male	1384 (66.1%)
Female	711 (33.9%)
Resides in high-income countries (*n* = 2095)	1294 (61.8%)
Median APACHE II score (*n* = 2077)	18 (13, 22)
Pupil reactivity (*n* = 1992)	
Both reactive	1508 (75.7%)
One reactive	154 (7.7%)
Both unreactive	330 (16.6%)
Median LIPS (*n* = 2095)	2.00 (0.00, 4.50)
GCS motor score (*n* = 2021)	
1–4	1,253 (62.0%)
5–6	768 (38.0%)
GCS score (*n* = 2016)	
3–5	735 (36.5%)
6–8	633 (31.4%)
9–15	648 (32.1%)
Highly pathological CT scan[§] (*n* = 2058)	1044 (50.7%)
Neuroworsening[#] (*n* = 2093)	962 (46.0%)
Mode of mechanical ventilation (*n* = 2052)	
Volume controlled	964 (47.0%)
Pressure controlled	295 (14.4%)
SIMV	234 (11.4%)
BiPAP	146 (7.1%)
ASV	35 (1.7%)
CPAP	56 (2.7%)
Other (not specified)	105 (5.1%)
Spontaneous (assisted ventilation) breathing	43 (2.1%)
Gas exchanges and respiratory settings/parameters	
Tidal volume (*n* = 1880), ml	480 (432, 520)
Tidal volume per body weight (*n* = 1880), *ml/kg*	6.46 (5.73, 7.33)
PEEP (*n* = 1943), *cmH2O*	5(5, 8)
PaO2 (*n* = 1916), *mmHg*	113 (92, 149)
PaO2/FiO2 (*n* = 1908)	307 (227, 397)
PaCO2 (*n* = 1918), *mmHg*	38 (34, 42)
Driving pressure (*n* = 1209), *cmH2O*	9(7, 12)
Compliance (*n* = 1197), *ml/cmH2O*	51 (40, 71)
Mechanical power (*n* = 970), *J/min*	12.7 (9.7, 16.9)
ICP and pulmonary complications	
Lowest ICP (*n* = 747), *mmHg*	4.0 (2.0, 8.0)
Highest ICP (*n* = 754), *mmHg*	15 (10, 20)
Presence of ICP > 20 (*n* = 754), *mmHg*	171 (22.7%)
Pneumonia (*n* = 1397)	36 (2.6%)
Pneumothorax (*n* = 1400)	76 (5.4%)
Pleural effusion (*n* = 1400)	212 (15.1%)
Atelectasis (*n* = 1399)	324 (23.2%)
Pulmonary edema (*n* = 1400)	44 (3.1%)
ARDS (*n* = 1931)	478 (24.8%)
Mild	286 (14.8%)
Moderate	170 (8.8%)
Severe	22 (1.1%)

Data are *n* (%) or *n/N* (%) or median (25th and 75th percentile, p25-p75). *GCS* Glasgow Come Scale, *LIPS* Lung injury prediction score. [§]Defined as Marshall classification 3 or more (for patients with TBI), Fisher grade 3 or more (for patients with SAH), ASPECTS score 6 or less (for patients with IS), ICH score 4 or more (for patients with ICH). [#]Defined as a spontaneous GCS motor score decrease of 2 points or more compared with the previous examination or a new loss of pupillary reactivity, development of pupillary asymmetry of at least 2 mm, or deterioration in neurological or CT status sufficient to warrant immediate medical or surgical intervention during the first week of the ICU stay

SIMV synchronized intermittent mandatory ventilation, *BiPAP* bilevel positive airway pressure, *ASV* adaptive support ventilation, *CPAP* continuous positive airway pressure, *ARDS* acute respiratory distress syndrome (using 2012 Berlin definition), *ICP* intracranial pressure, *VAP* ventilator-associated pneumonia defined by Clinical Pulmonary Infection Score (CPIS score), *PC* pulmonary complication

[*] Data at ICU admission (i.e., first measurements) are collected at day 0 when patients were admitted at ICU before 6 pm or at the day after (i.e., day 1) when admitted at ICU after 6 pm

Ventilatory parameters

Ventilatory settings on admission are presented in Table 1. The most common mode of ventilation was volume-controlled ventilation ($n = 964$, 47%), followed by pressure-controlled ventilation ($n = 295$, 14.4%). On admission, LPS strategies were adopted in 1082 (86.1%) cases. Median TV was 480 (432–520) mL, TV/PBW 6.5 (5.7–7.3) mL/Kg, PEEP 5 (5–8) cmH_20, RR 15 (14–18)/min, and FiO_2 0.40 (0.30–0.50). Median Ppeak was 20 (17–25) cmH_20, Pplat 15 (13–18) cmH_20, DP 9 (7–12) cmH_20 and mechanical power 12.7 (9.7–16.9) J/min. Median respiratory system compliance was 51 (40–71) ml/cmH_20, PaO_2 was 113 (92–149) mmHg, $PaCO_2$ 38 (34–42) mmHg and PaO_2/FiO_2 was 307 (227–397).

The distribution of the ventilatory settings and parameters is depicted over time in Fig. 1 (and electronic supplementary figure 3) and described in electronic supplementary table 2. Over the study period, information about LPS usage was available in 1389 patients, with a total number of 6468 measurements. LPS were used at least once in 1273 (91.6%) patients and for a total of 5360 (82.8%) measurements.

Ventilation settings according to intracranial hypertension

A total of 14,977 measurements of ICP were obtained over the study period in 820 patients (Table 1). The median ICP value in the morning was 10 (6–14) mmHg, the highest ICP was 15 (11–20) mmHg. Episodes of intracranial hypertension were observed in 1116 (22.3%) measurements (electronic supplementary

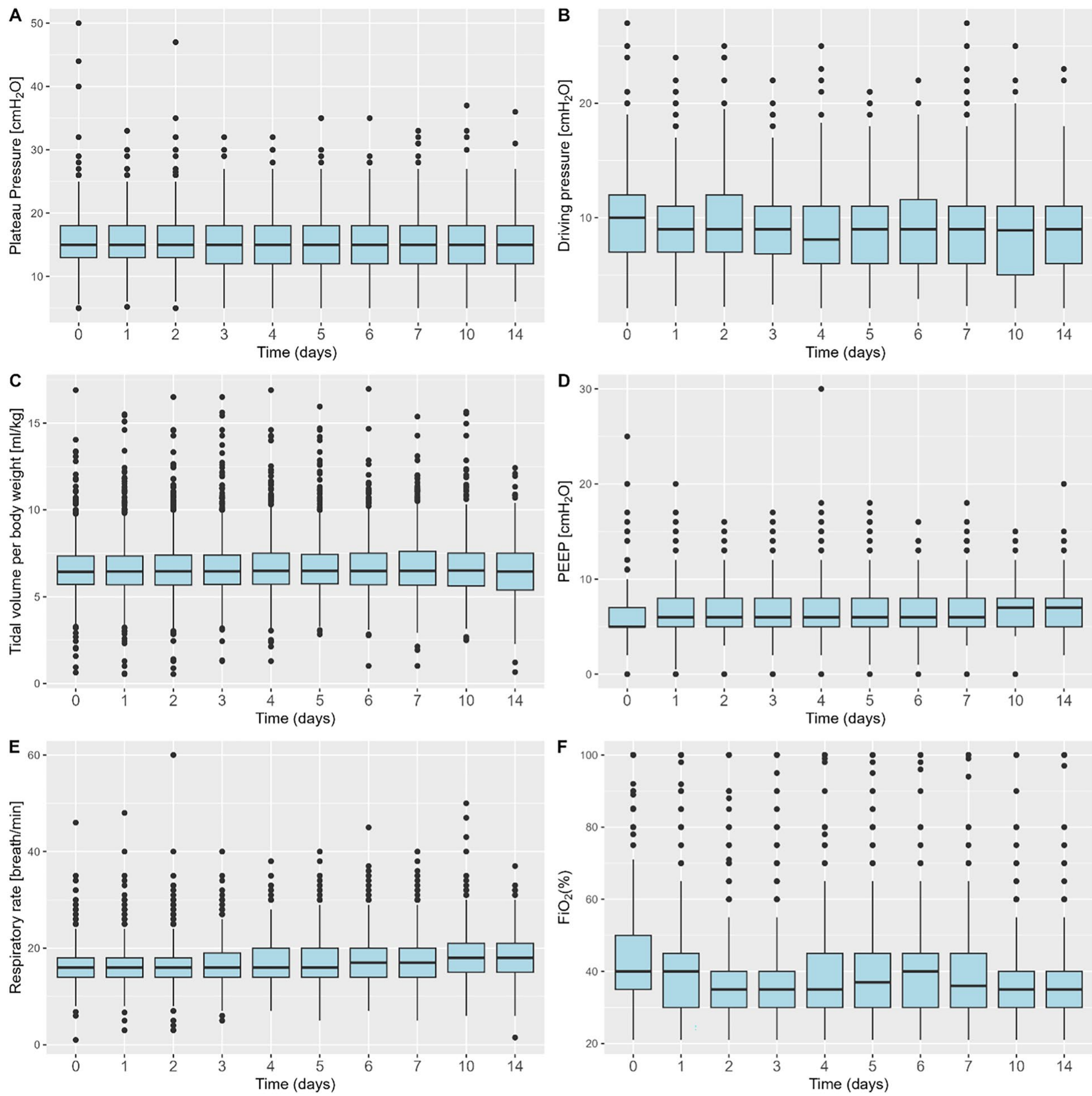

Fig. 1 Boxplots of mechanical ventilation setting parameters during ICU stay. Boxplots for mechanical ventilation settings/parameters were collected daily till day 7 since intensive care unit (ICU) admission and at days 10 and 14 for all patients. The lower and upper limits of the boxes correspond to the 25th percentile and the 75th percentile, respectively. The horizontal lines inside the box represent the median (50th percentile). The points represent the values higher or lower than the box limits by more than 1.5 times the interquartile range (IQR: the difference between the 75th and the 25th percentile). Panel **A** plateau pressure, panel **B** driving pressure, panel **C** tidal volume per body weight, panel **D** positive and expiratory pressure (PEEP), panel **E** respiratory rate, panel **F** FiO_2

table 1) and at least once in 171 (22.7%) patients. In the presence of intracranial hypertension, no differences were observed across the ventilatory settings (electronic supplementary figures 4 and 5).

Ventilation settings differences among countries

The distribution of each ventilator setting/parameter in the participating countries is reported in Fig. 2 and electronic supplementary figures 6-8. The highest country-to-country variability was observed for mechanical

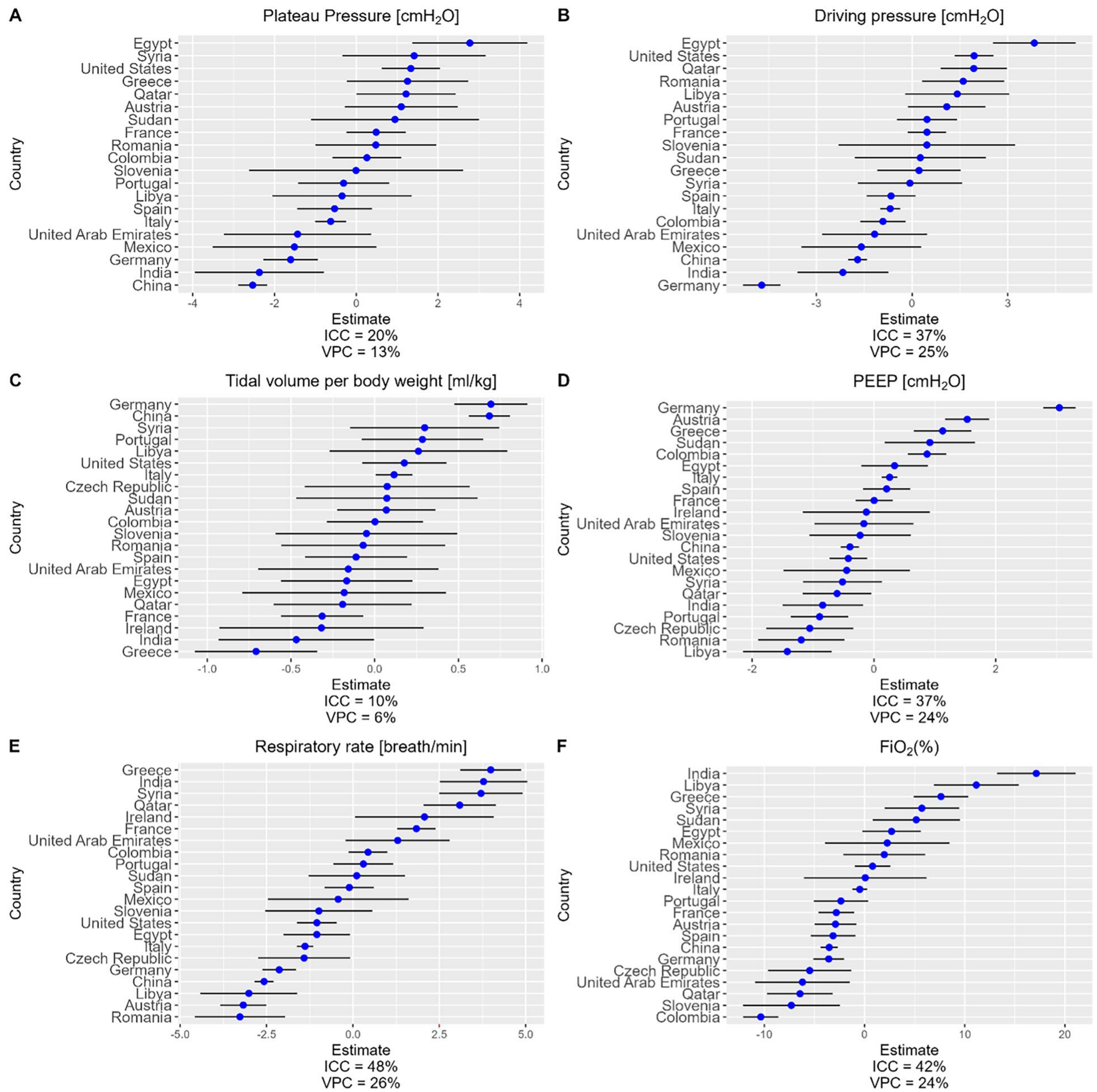

Fig. 2 Caterpillar plots of between-country variability for every ventilator setting parameter. Estimated random effects of every country (blue dots) with the corresponding 95% confidence intervals (black lines) from a linear mixed-effects model using individuals and countries as random intercepts and adjusted for age (per decade), sex, time of ventilator parameter collection during the ICU stay (from day 0/day 1 and daily till day 7 and day 10 and day 14), type of brain injury, Glasgow coma motor score, PaO_2/FiO_2 ratio at admission, and pupillary reactivity as fixed-effects. Random effects point and interval estimates close to zero represent countries with a ventilator parameter/setting close to the overall mean. Random effects and interval estimates below or above zero represent countries with a lower or higher ventilator measure set below or above the overall mean, respectively. The intraclass correlation coefficients (ICCs) and the variance partition coefficients (VPCs) are also reported. Higher values of ICCs and VPCs (closer to one) suggest a higher country-level contextual effect. Panel **A** plateau pressure, panel **B** driving pressure, panel **C** tidal volume per body weight, panel **D** positive and expiratory pressure (PEEP), panel **E**: respiratory rate, panel **F** FiO_2

power (VPC 35%) and Peak, PEEP, driving pressure, and RR (VPC from 23 to 26%), while the lowest was reported for Pplat (VPC 13%) and TV/PBW (VPC 6%) (Fig. 2 and electronic supplementary figures 7-8). We also assessed the degree of homogeneity in the patients' longitudinal ventilator measures within the same country and found moderate similarity for PaO_2 (ICC 60%), mechanical power (ICC 51%), respiratory rate (ICC 48%) and FiO_2

(ICC 42%). The lowest similarity and the lowest country contextual effect were obtained for $PaCO_2$, Pplat and TV/PBW, with the corresponding estimated ICCs of 25%, 20% and 10%, respectively (Fig. 2, electronic supplementary figures 7-8).

Association of ventilator settings/parameters with mortality and neurological outcome

A total of 597 (29.2%) patients died in the ICU, and mortality at 6-month follow-up was 42% (95% CI = 40–45%). Most of the ventilatory measures were individually associated with ICU mortality. In particular, an increased probability of mortality was observed for increasing values of Ppeak (HR = 1.43, 95% CI = 1.28–1.61), Pplat (HR = 1.50, 95% CI = 1.27–1.78), and DP (HR = 1.41, 95% CI = 1.18–1.69) (Fig. 3, electronic supplementary figures 9-10). The probability of mortality over time was lower for patients with higher values of TV/PBW (HR = 0.86, 95% CI = 0.77–0.96), while PEEP, respiratory rate and FiO_2 showed a U-shaped non-linear association with ICU mortality rate (Fig. 3 and electronic supplementary table 4, electronic supplementary figure 9). When the ventilator measures were included in two global Cox adjusted models, one for settings and another one for parameters, their association with ICU mortality was confirmed (electronic supplementary material 4), except for MP. The results demonstrated consistency in their association with 6-month mortality (electronic supplementary material 4). An unfavorable GOSE was observed in 1254 (69.3%) out of 1807 patients. Among ventilatory settings, those suggested to be individually associated with GOSE (electronic supplementary figures 10-11 and electronic supplementary material 4) were PEEP (OR = 1.23, 95% CI = 1.05–1.44) and FiO2 (OR = 1.23, 95% CI = 1.08–1.39). Among ventilatory parameters, only driving pressure (DP) suggested an association with GOSE (OR = 1.35, 95% CI = 1.14–1.59) (electronic supplementary material 4). When all ventilatory settings and parameters were considered for a global assessment into two separate adjusted models, the magnitude of the effects resulted diluted, except for a borderline signal for FiO_2 (electronic supplementary material 4).

Discussion

In this large, international, prospective cohort study, we observed that LPS were often adopted in ABI patients, both on admission and during their ICU stay, regardless of the presence of increased ICP. High to moderate variability across different countries was estimated, especially regarding DP and mechanical power. Higher Pplat, Ppeak and DP and lower TV/PBW were linearly associated with ICU- and 6-month mortality, while PEEP, RR and FiO_2 showed a U-shaped association. No clear relation of these measures with neurological outcome was depicted.

Over the last decades, research has importantly focused on the need to adopt LPS [29–31], which include the use of low TV, Pplat, and moderate-high PEEP to prevent lung damage and to reduce morbidity and mortality in general ICU patients [2, 32]. However, safety concerns regarding the potential detrimental effects of these strategies on cerebral perfusion pressure and intracranial pressure [2] have traditionally limited their applications in the ABI population [33]. The concept of lung-brain cross-talk in this context remains a critical topic, characterized by limited evidence and challenging clinical scenarios [1]. For instance, LPS incorporating permissive hypercapnia may be poorly tolerated in patients with ABI and elevated intracranial pressure, while increased intrathoracic pressure could impair cerebral hemodynamics [1].

The concept of LPS has been progressively translated into the ABI population over the last decade and has led to a progressive change in clinical practice. Tejerina et al. [34], in a retrospective study of 4152 patients, found that the proportion of ABI patients receiving a protective lung ventilation strategy increased over time: 47% in 2004, and 65% in 2016, with progressively higher values of PEEP used (and a lower rate of zero PEEP-ZEEP) as well as lower values of TV/Kg PBW. Our results confirm this trend; neuro-intensivists seem to pay particular attention to Pplat, DP and tidal volume/PBW values, which were within "protective" ranges in our cohort [28]. This is also likely because the values of compliance of the respiratory system and PaO_2/FiO_2 suggest that respiratory mechanics were generally well preserved in our population. In particular, the median TV/PBW at admission was extremely low, e.g., 6.5 ml/Kg PBW, whereas in the PROVENT [35] study median TV/PBW was 7.9 mL/kg with no differences between patients at risk of ARDS and those not at risk.

Similarly, the median PEEP value in our study was 5 cmH20, similar to in the PROVENT study, and only 0.1% were ventilated using a ZEEP, suggesting a progressive adherence to the latest guidelines [14]. Despite we observed a slight progressive increase in Ppeak and Pplat, from day 1 to day 7, these values remained below the thresholds described in the literature as at risk for complications [3]. Our results show an important change, with the application of LPS even in ABI patients, as suggested by previous sub-analyses and retrospective large databases [36]. However, it is also important to highlight that we found considerable variability across different countries in the use of these strategies, especially regarding more novel and composite parameters such as mechanical power and driving pressure, but with lower

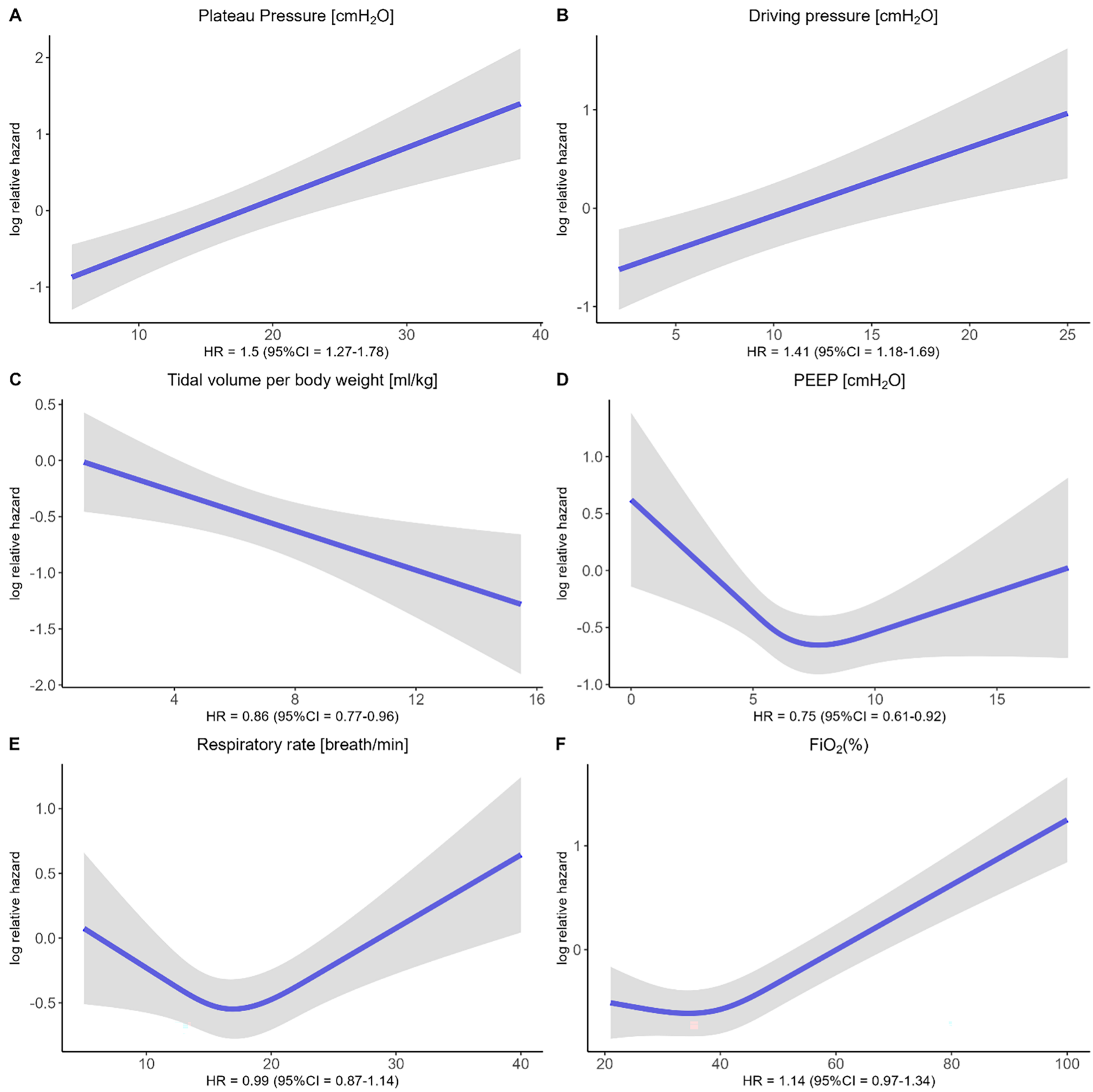

Fig. 3 The relation between every mechanical ventilator setting parameter and the ICU mortality. The association between every mechanical ventilator setting/parameter (x-axis) on the logarithm of the relative hazard (y-axis) estimated by time-dependent Cox proportional hazard regressions adjusted for age, sex, type of brain injury, Glasgow coma motor score and pupillary reactivity. Predicted values (blue lines) were estimated using the reference categories for the categorical adjustment predictors (e.g., male individuals for sex) and using medians for continuous predictors (e.g., age). Pointwise 95% confidence limits (shaded grey areas) are also shown. The adjusted hazard ratios (HRs) for the 75th percentile of every mechanical ventilator setting/parameter versus the 25th percentile with 95% confidence intervals are also reported using the linear or non-linear term (i.e., three-knot restricted cubic spline). Panel **A** plateau pressure, panel **B** driving pressure, panel **C** tidal volume per body weight, panel **D** positive and expiratory pressure (PEEP), panel **E** respiratory rate, panel **F** FiO_2

heterogeneity regarding the values of TV/PBW and Pplat. This might be related to the presence of stronger and more established evidence for the use of low TV and Pplat in the literature available [31, 37, 38] and less clear for other parameters. The variability observed in our results is also a clear consequence of the lack of strong evidence provided by the latest ESICM Guidelines on MV in ABI patients [14].

Interestingly, when ICP was increased, no changes in the ventilatory parameters were observed. However,the median highest ICP value during the day was 15 (11–20) mmHg, thus suggesting that ICP was overall well controlled.

We finally explored the association between ventilatory measures on clinical outcomes, finding that the majority of ventilatory settings/parameters are associated with both ICU and 6-month mortality. These results are in line with a recent secondary analysis of the TTM2 trial including 1848 patients with post-anoxic brain injury (3), but are extremely novel in the ABI population.

High Pplat, Ppeak, and DP were linearly associated with mortality, confirming previous findings from the general ICU population; PEEP, RR and FiO_2 showed a U-shaped curve association, suggesting the need to individualize these measures, in line with the evidence from the general ICU population [39].

Interestingly, our model shows that higher TV/PBW is associated with decreased mortality. However, it is important to highlight that TV was maintained quite low in our cohort, with an estimated IQR of 5.7–7.3 ml/PBW. Despite observational data, we cannot draw any conclusion on causal relationship, we can only speculate that while protective limits for Pplat, DP are essential, very low TV may not necessarily be beneficial in this population. Adequate TV may help stabilize and control $PaCO_2$ levels [40]; however, after adjusting our model for $PaCO_2$, no significant differences in measured HR were observed, indicating that further studies are needed to better understand this association.

This finding aligns with the recent PROLABI randomized controlled trial [41], which did not demonstrate that ventilation with lower TV and higher PEEP, compared to conventional ventilation, improved clinical outcomes in patients with ABI.

We found no potential effect of ventilation strategies on the long-term neurological outcome. This may be due to several factors, including the limitations of the GOSE scale itself, which grades disability, but lacks a detailed assessment of neurocognitive dysfunction and quality of life. Furthermore, numerous ICU and post-ICU factors, such as physiotherapy, rehabilitation, and healthcare system organization for post-ICU care, can significantly influence neurological outcomes but were not addressed in our study. Interestingly, FiO_2 was associated with neurological outcomes, underscoring the critical importance of precise titration of oxygen targets in this population [42–44].

Strengths and limitations

To our knowledge, this is the first prospective international multicenter study which focused on the description of ventilatory settings of ABI patients requiring invasive MV and their effect on outcomes in the specific population. This study includes a high number of centers from different countries, thus providing a comprehensive picture of the clinical practice worldwide and paving the way to a generalization of our results as well as to the uniformity of care all over the globe.

However, our study also presents several limitations that need to be mentioned. Importantly, this is an observational study, and no conclusions about causality can be drawn from our findings. Indeed, while the results on the associations with mortality and neurological outcomes were adjusted for confounders using robust statistical models, they should be interpreted with caution.

In addition, the inclusion timeframe overlaps with the COVID-19 pandemic; therefore, we cannot entirely exclude the possibility that this period influenced the occurrence of pulmonary complications or altered workflows, resource allocation, or other pandemic-related factors. Although this study was designed as a planned multicenter effort with detailed information on ICU stay and clinical outcomes, specific and granular information is lacking, such as the presence of chest or spinal cord trauma. In addition, ventilatory settings were recorded only once daily, which prevented detailed analysis of dynamic changes in response to clinical events or complications. Similarly, more comprehensive data on non-invasive ventilation, assisted ventilation, weaning processes, physiotherapy, and post-acute care would have provided valuable insights and further strengthened our findings. This approach was taken to balance the collection of meaningful data with minimizing the workload for participating centers, particularly in the absence of funding to support recruitment efforts.

Despite these limitations, our findings offer valuable insights that may help to guide clinical decision-making and improve patient stratification in future RCTs. Our results highlight the need for well-designed, adequately powered randomized studies to optimize care and outcomes in this challenging patient population.

Conclusions

In this large cohort of ABI mechanically ventilated patients, we found that LPS were commonly used, with considerable variability across different countries. Several ventilatory settings were associated with ICU and 6-month mortality, but not with neurological outcomes. Personalized ventilatory targets and their impact on survival need to be further assessed in this heterogeneous population considering variability among centers and countries.

Supplementary Information
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Data availability
The data supporting the study findings are available upon reasonable request, after approval by the study management committee. Only deidentified and anonymized data will be shared, in compliance with GDPR and data protection regulations and a data dictionary defining each field in the set. Related documents, such as the study protocol, statistical analysis plan, and informed consent form, will also be available.

Declarations

Conflicts of interest
CR received fees for lectures from BD, not related to this work. GC reports fees as a Speakers' Bureau Member and Advisory Board Member from Integra and Neuroptics, all outside the submitted work. FST reports fees as an Advisory Board Member for Neuroptics, Nihon Khoden and Eurosets. JGL reports consulting fees received from Cellenkos. RH reports fees from BD, Zoll, Integra, and Neuroptics. The other authors have no COI to declare.

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