Evolution Over Time of Ventilatory Management and Outcome of Patients With Neurologic Disease*

Evolution Over Time of Ventilatory Management and Outcome of Patients With Neurologic Disease*

Eva E. Tejerina, MD, PhD[1]
Paolo Pelosi, MD, FERS[2]
Chiara Robba, MD, PhD[2]
Oscar Peñuelas, MD, PhD[1]
Alfonso Muriel, MSc, PhD[3]
Deisy Barrios, MD[4]
Fernando Frutos-Vivar, MD[1]
Konstantinos Raymondos, MD[5]
Bin Du, MD[6]
Arnaud W. Thille, MD[7]
Fernando Ríos, MD[8]
Marco González, MD[9]
Lorenzo del-Sorbo, MD[10]
Maria del Carmen Marín, MD[11]
Bruno Valle Pinheiro, MD[12]
Marco Antonio Soares, MD[13]
Nicolas Nin, MD, PhD[14]
Salvatore M. Maggiore, MD[15]
Andrew Bersten, MD[16]
Pravin Amin, MD[17]
Nahit Cakar, MD[18]
Gee Young Suh, MD[19]
Fekri Abroug, MD[20]
Manuel Jibaja, MD[21]
Dimitros Matamis, MD[22]
Amine Ali Zeggwagh, MD[23]
Yuda Sutherasan, MD[24]
Antonio Anzueto, MD[25]
Andrés Esteban, MD, PhD[1]
on behalf of the VENTILA Group

***See also p. 1200.**

OBJECTIVES: To describe the changes in ventilator management over time in patients with neurologic disease at ICU admission and to estimate factors associated with 28-day hospital mortality.

DESIGN: Secondary analysis of three prospective, observational, multicenter studies.

SETTING: Cohort studies conducted in 2004, 2010, and 2016.

PATIENTS: Adult patients who received mechanical ventilation for more than 12 hours.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Among the 20,929 patients enrolled, we included 4,152 (20%) mechanically ventilated patients due to different neurologic diseases. Hemorrhagic stroke and brain trauma were the most common pathologies associated with the need for mechanical ventilation. Although volume-cycled ventilation remained the preferred ventilation mode, there was a significant ($p < 0.001$) increment in the use of pressure support ventilation. The proportion of patients receiving a protective lung ventilation strategy was increased over time: 47% in 2004, 63% in 2010, and 65% in 2016 ($p < 0.001$), as well as the duration of protective ventilation strategies: 406 days per 1,000 mechanical ventilation days in 2004, 523 days per 1,000 mechanical ventilation days in 2010, and 585 days per 1,000 mechanical ventilation days in 2016 ($p < 0.001$). There were no differences in the length of stay in the ICU, mortality in the ICU, and mortality in hospital from 2004 to 2016. Independent risk factors for 28-day mortality were age greater than 75 years, Simplified Acute Physiology Score II greater than 50, the occurrence of organ dysfunction within first 48 hours after brain injury, and specific neurologic diseases such as hemorrhagic stroke, ischemic stroke, and brain trauma.

CONCLUSIONS: More lung-protective ventilatory strategies have been implemented over years in neurologic patients with no effect on pulmonary complications or on survival. We found several prognostic factors on mortality such as advanced age, the severity of the disease, organ dysfunctions, and the etiology of neurologic disease.

KEY WORDS: mechanical ventilation; mortality; neurologic patients; prognosis factors; pulmonary complications

Patients with neurologic conditions account for the 10–15% of all ICU admissions (1); among these coma is the main reason for initiation of mechanical ventilation, occurring in nearly 20% of cases (2, 3). Several

DOI: 10.1097/CCM.0000000000004921

studies involving neurocritical care patients have suggested that there is considerable variability in mortality among countries and individual centers (4–13); furthermore, survivors often harbor permanent neurologic impairment with various degrees of disability (14, 15). To date, only a few specific interventions have definitively proven to be able to improve outcome in neurocritical care patients, and potential beneficial effects of currently used treatments are likely less relevant than expected (16).

However, the patients'outcome is not only related to the primary neurologic damage but also to the development of extracranial organ derangement; among these, respiratory failure is one of the most frequent systemic dysfunctions (17).

Mechanical ventilation is a main component of early treatment of neurocritically ill patients, with the aim to improve gas exchange, allows tight control of respiratory variables, and not adversely affects cerebral hemodynamics. A recent study showed that outcomes of mechanically ventilated patients have improved over time (3). However, mechanically ventilated patients with neurologic disease have higher mortality than other critically ill patients (1). Also, ventilatory management of neurologic critically ill patients can be very challenging as it is aimed to minimize ventilator-induced lung injury, and at the same time to optimize cerebral oxygenation avoiding elevations in intracranial pressure due to hypercapnia (18). Ventilatory targets of lung-protective ventilation are often in conflict with cerebral physiology (19), and therefore patients with neurologic injuries have been typically excluded from the big trials regarding lung-protective strategies. As a result, the effect of ventilatory management on neurologic patients' outcome has been scarcely evaluated.

The primary aim of this study was to describe the changes in ventilatory management over time in patients with neurologic disease admitted to the ICU. Secondary objective was to estimate the factors associated with 28-day hospital mortality in this cohort of patients.

MATERIALS AND METHODS

Study Design

We performed a secondary analysis of three prospective, observational, multicenter studies conducted in 2004 (20), 2010 (3), and 2016 (21) on adult patients who received mechanical ventilation for more than 12 hours. The protocol was approved by the research ethics board of each participating institution and need for informed consent was obtained according to local rules. For the purpose of this analysis, we included mechanically ventilated patients due to different neurologic diseases. Data collection procedure has been previously described in detail (21). Patients were followed-up until hospital discharge.

Patient's Classification

Patients were defined as primarily neurologic patients if they had a reduced level of consciousness as a result of a primary brain insult. Patients with a diagnosis of cerebrovascular accident of ischemic or hemorrhagic etiology or with brain trauma with or without multisystemic trauma were therefore included in this analysis. We also included patients with a depressed level of consciousness as a result of metabolic abnormalities or intoxication/overdose. We excluded patients with a Glasgow Coma Scale (GCS) score greater than 13 points in the 2 first days of mechanical ventilation. The GCS was assessed at admission in the absence of sedative drugs.

Statistical Analysis

Data are expressed as mean (SD), median (interquartile range), and absolute and relative frequencies as appropriate. We used the Shapiro-Wilk test to assess continuous data for a normal distribution. To compare continuous data between cohorts, a lineal regression was performed and to compare categorical variables, a logistic regression was performed.

To estimate a predictive model to assess 28-day mortality, we performed a logistic regression model only with the data from study carried out in 2016 to avoid bias associated to time. The predictive model included the following variables: baseline variables—age (categorized as < 65 yr, 65–74 yr, older than 75 yr), Simplified Acute Physiology Score (SAPS) II (categorized as higher than 50 points and lower than 50 points), cause of neurologic disease (entered as a dummy variable with following categories: overdose [as reference category], metabolic, hemorrhagic stroke, ischemic stroke, trauma, and other causes) and events occurred within first 48 hours after beginning of mechanical ventilation: hypercapnia (entered as a dummy variable with following categories: normocapnia and

normal pHa [as reference category], compensated hypercapnia, and hypercapnic acidosis [22]), and organ dysfunction (cardiovascular, renal, hematological, hepatic, respiratory) defined as a Sequential Organ Failure Assessment score higher than 2 points.

We used a backward stepwise logistic regression to consider combinations of variables for inclusion in our final model using p value of less than or equal to 0.05 for a statistical significance. We also compared the discriminative power of the model to predict 28-day mortality by calculating the area under the receiver operating characteristic curve. To estimate the points assigned to each significant variable, we set the constant, B, as the number of regression units that corresponds to 1 point. We then computed the points for each risk factor's risk categories as the difference in regression units between each category and its base category divided by B rounded. The prediction score was calculated by a sum of individual values of each category. The final score ranges from 0 to 9 points, with higher scores indicating a greater risk of death within 28 days after admission.

All analyses were performed using Stata 14.0 (Stata Corp., College Station, TX).

RESULTS

Characteristics of Included Patients

Among the 20,929 patients enrolled, we included 4,152 (20%) mechanically ventilated patients due to different neurologic diseases. Baseline characteristics of the patients included from each study are shown in **Table 1**. Hemorrhagic stroke and brain trauma were the most common pathologies associated with the need for mechanical ventilation.

Ventilator Management

Table 2 shows the evolution of the ventilator settings in the three studies over time (from 2004 to 2016). Although volume-cycled ventilation remained the preferred ventilation mode, there was an overall significant ($p < 0.001$) increment in the use of pressure support ventilation.

Protective lung ventilation (low tidal volume and high positive end-expiratory pressure [PEEP]) was increasingly applied from 2004 to 2016. The proportion of patients receiving ventilation strategy with pressure/volume limitation was increased over the time: 47% in 2004, 63% in 2010, and 65% in 2016 ($p < 0.001$). The duration of ventilatory support using protective ventilation strategies increased over time: 406 days per 1,000 mechanical ventilation days in 2004, 523 days per 1,000 mechanical ventilation days in 2010, and 585 days per 1,000 mechanical ventilation days in 2016 ($p < 0.001$).

Disconnection From Mechanical Ventilation

The onset of weaning was the time that the physician in charge considered the patient likely to resume and sustain spontaneous breathing after they met standard criteria for weaning readiness. No significant changes were observed in the percentage of patients who initiated the weaning from mechanical ventilation (60% in 2004, 64% in 2010, and 62% in 2016) and those who were extubated on a scheduled basis (86% in 2004, 81% in 2010, and 85% in 2016). Among the methods for weaning from mechanical ventilation, the use of spontaneous breathing trial as first attempt decreased from 2004 to 2016 (from 72% in 2004 to 51% in 2016; $p < 0.001$). Among patients who failed the first attempt of weaning, there was a statistically significant reduction in the use of synchronized intermittent mandatory ventilation with (from 21% in 2004 to 8% in 2016; $p < 0.001$) or without pressure support (from 6% in 2004 to 2% in 2016; $p < 0.001$) over time.

There was a significant trend toward a higher use of noninvasive positive pressure ventilation as preventive or as treatment of postextubation respiratory failure: 3% in 2004, 4% in 2010, and 7% in 2016 ($p = 0.010$).

Reintubation rate within the first 48 hours after scheduled extubation was not statistically different in three periods: 10% in 2004, 9% in 2010, and 8% in 2016 ($p = 0.305$).

There was a higher occurrence rate ($p < 0.001$) of unplanned extubation in 2010 (8%) versus 2004 (3%) and 2016 (4.5%) versus 2004, but with similar rate of reintubation: 26% in 2004, 24% in 2010, and 26% in 2016 ($p = 0.913$).

Performance of tracheotomy was similar among the three cohorts: 17% in 2004, 19% in 2010, and 16% in 2016 ($p = 0.181$). Also, median time from intubation to tracheotomy was similar over time: 12 days (25th percentile [P_{25}]–75th percentile [P_{75}]; 7–17 d) in 2004, 12 days (P_{25}–P_{75}: 9–16 d) in 2010, and 9 days (P_{25}–P_{75}: 6–12 d) in 2016 ($p = 0.789$). There were not differences in the type of tracheotomy performed; percutaneous tracheotomy remained the preferred method in all the groups: 56% in 2004, 57% in 2010, and 56% in 2016 ($p = 0.917$).

TABLE 1.
Comparison of Baseline Characteristics Between Three Cohorts

Baselines Characteristics	2004 ($n = 938$)	2010 ($n = 1,574$)	2016 ($n = 1,640$)
Age, yr, mean (SD)[a]	54 (18)	56 (18)	57 (19)
Female, *n* (%)[b]	380 (40)	606 (38)	672 (41)
Body mass index, kg/cm^{2}[c]	26 (5)	26 (5)	26 (5)
Simplified Acute Physiology Score II, points, mean (SD)[d]	44 (16)	46 (16)	48 (18)
Neurologic disease, *n* (%)			
Hemorrhagic stroke[e]	308 (33)	470 (30)	434 (26)
Brain trauma[f]	227 (24)	302 (19)	379 (23)
Intoxication/overdose[g]	148 (16)	211 (13)	198 (12)
Ischemic stroke[h]	116 (12)	214 (14)	199 (12)
Metabolic[i]	125 (13)	265 (17)	288 (18)
Other cause (includes infection of CNS, seizures, and miscellaneous)[j]	14 (1.5)	112 (7)	142 (9)
Glasgow Coma Scale at admission, points, mean (SD) (only patients without sedative drugs)[k]	9 (4)	8 (4)	6 (4)

[a]$p = 0.009$ for comparison 2004 vs 2010; $p < 0.001$ for comparison 2004 vs 2016; and $p = 0.336$ for comparison 2010 vs 2016.
[b]$p = 0.318$ for comparison 2004 vs 2010; $p = 0.818$ for comparison 2004 vs 2016; and $p = 0.152$ for comparison 2010 vs 2016.
[c]$p = 0.732$ for comparison 2004 vs 2010; $p = 1.000$ for comparison 2004 vs 2016; and $p = 0.365$ for comparison 2010 vs 2016.
[d]$p = 0.006$ for comparison 2004 vs 2010; $p < 0.001$ for comparison 2004 vs 2016; and $p = 0.058$ for comparison 2010 vs 2016.
[e]$p = 0.019$ for comparison 2004 vs 2010; $p = 0.001$ for comparison 2004 vs 2016; and $p = 0.032$ for comparison 2010 vs 2016.
[f]$p = 0.003$ for comparison 2004 vs 2010; $p = 0.530$ for comparison 2004 vs 2016; and $p = 0.037$ for comparison 2010 vs 2016.
[g]$p = 0.101$ for comparison 2004 vs 2010; $p = 0.008$ for comparison 2004 vs 2016; and $p = 0.257$ for comparison 2010 vs 2016.
[h]$p = 0.378$ for comparison 2004 vs 2010; $p = 0.862$ for comparison 2004 vs 2016; and $p = 0.216$ for comparison 2010 vs 2016.
[i]$p = 0.019$ for comparison 2004 vs 2010; $p = 0.005$ for comparison 2004 vs 2016; and $p = 0.586$ for comparison 2010 vs 2016.
[j]$p < 0.001$ for comparison 2004 vs 2010; $p < 0.001$ for comparison 2004 vs 2016; and $p = 0.106$ for comparison 2010 vs 2016.
[k]$p = 0.047$ for comparison 2004 vs 2010; $p < 0.001$ for comparison 2004 vs 2016; and $p = 0.01$ for comparison 2010 vs 2016.

Outcomes

Table 3 shows the complications occurring during ventilatory support and outcome in three cohorts. A significant decrease in the duration of ventilatory support in the last study group was observed. There were no differences in the length of stay in the ICU, mortality in the ICU, and mortality in hospital from 2004 to 2016.

A decision for withdrawal/withholding support occurred in 16% of patients (249/1,574 patients) in 2010, and 14% (232/1,634 patients) in 2016 ($p = 0.198$). Hospital mortality was 84% in 2010 and 80% in 2016 in patients with withdrawal/withholding care.

Predictive Score for 28-Day Mortality

Mortality at day 28 in 2016 was 31%. **Table 4** shows the variables explored, registered within first 48 hours, and their association associated with mortality. On the basis of these results, we generated a score for prediction of 28-day mortality including the following variables: age, SAPS II, neurologic disease, and number of organ dysfunctions within 2 first days (**Fig. 1**). A comparison of the ROC curves between SAPS II and the predictive model scores is shown in **Appendix 1** (http://links.lww.com/CCM/G193).

TABLE 2.
Comparison of Ventilator Setting and Arterial Blood Gases Between Three Cohorts

Ventilator Setting and Arterial Blood Gases	2004 (*n* = 938)	2010 (*n* = 1,574)	2016 (*n* = 1,640)
Mode of ventilation, days of mode per 1,000 days of mechanical ventilation[a]			
Volume controlled	516	367	307
Pressure support	123	226	253
SIMV	19	32	51
SIMV-pressure support	116	118	84
Pressure-controlled ventilation	82	78	132
Airway pressure release ventilation/bilevel positive airway pressure	48	54	79
Pressure-regulated volume control	75	101	66
Other mode	21	24	28
Tidal volume[a]			
mL, mean (SD)	570 (114)	517 (105)	486 (99)
mL/kg PBW, mean (SD)	9.1 (2)	8.3 (1.8)	8.0 (1.7)
Proportion of days of ventilatory support with[a]			
< 6 mL/kg PBW	4%	6%	8%
6–8 mL/kg PBW	26%	43%	48%
8–10 mL/kg PBW	42%	36%	35%
> 10 mL/kg PBW	28%	14%	9%
Positive end-expiratory pressure, cm H_2O, mean (SD)[a]	4.1 (3.7)	6.2 (2.6)	6.2 (2.2)
Proportion of days of ventilatory support with[a]			
< 5 cm H_2O	72%	58%	56%
5–10 cm H_2O	24%	36%	40%
10–15 cm H_2O	4%	5%	4%
> 15 cm H_2O	< 1%	< 1%	< 1%
Peak pressure, cm H_2O, mean (SD)[a]	25 (7)	23 (7)	22 (7)
Plateau pressure, cm H_2O, mean (SD)[a]	19 (5)	18 (6)	17 (5)
Driving pressure, cm H_2O, mean (SD)[a]	15 (5)	12 (5)	11 (4)
Respiratory rate, breaths/min, mean (SD)[a]	16 (5)	18 (5)	19 (5)

(*Continued*)

TABLE 2. (*Continued*).
Comparison of Ventilator Setting and Arterial Blood Gases Between Three Cohorts

Ventilator Setting and Arterial Blood Gases	2004 (*n* = 938)	2010 (*n* = 1,574)	2016 (*n* = 1,640)
Arterial blood gases, mean (SD)			
At start mechanical ventilation			
pHa[b]	7.39 (0.10)	7.37 (0.11)	7.36 (0.11)
$Paco_2$[c]	36 (9)	37 (10)	38 (11)
Pao_2/Fio_2[d]	272 (98)	280 (102)	257 (100)
Last day on mechanical ventilation			
pHa[e]	7.41 (0.08)	7.40 (0.09)	7.41 (0.10)
$Paco_2$[f]	36 (8)	38 (8)	38 (9)
Pao_2/Fio_2[g]	274 (93)	290 (94)	272 (89)

PBW = predicted body weight, SIMV = synchronized intermittent mandatory ventilation.
[a]$p < 0.001$ for all comparisons between years.
[b]$p < 0.001$ for comparison between 2004 vs 2010 and 2004 vs 2016; $p = 0.546$ for comparison between 2010 vs 2016.
[c]$p = 0.013$ for comparison between 2004 vs 2010; $p = 0.001$ for comparison between 2004 vs 2016; and $p = 1.00$ for comparison between 2010 vs 2016.
[d]$p = 0.272$ for comparison between 2004 vs 2010; $p = 0.002$ for comparison between 2004 vs 2016; and $p < 0.001$ for comparison between 2010 vs 2016.
[e]$p = 1.000$ for all comparisons between years.
[f]$p < 0.001$ for comparison between 2004 vs 2010 and 2004 vs 2016; $p = 0.468$ for comparison between 2010 vs 2016.
[g]$p = 0.009$ for comparison between 2004 vs 2010; $p = 1.00$ for comparison between 2004 vs 2016; and $p < 0.001$ for comparison between 2010 vs 2016.

DISCUSSION

In our analysis of three cohorts of mechanically ventilated patients due to neurologic diseases, we found that: 1) the use of protective lung ventilation (low tidal volume and high PEEP) is increasing over the years as well as the duration of protective lung strategies application; 2) patients' outcome did not change over time, except for a significant decrease in the duration of ventilatory support in the most recent study; and 3) the risk factors associated with 28-day mortality were age greater than 75 years, SAPS II greater than 50, the occurrence of organ dysfunction within first 48 hours after brain injury, and specific neurologic diseases such as hemorrhagic stroke, ischemic stroke, and brain trauma.

Non-neurologic organ dysfunctions are important predictors of outcome in neurocritical care patients, with the lung being one of the most vulnerable organs to the inflammatory cascade triggered by acute brain injury (17, 23, 24). Early physiologic derangements are known to be associated with worse outcome, and their timely correction could implement recovery (25, 26). However, conventional modalities of mechanical ventilation used in the management of lung injury such as permissive hypercapnia may worsen brain injury by causing vasodilation and increasing intracranial pressure; consequently, lung-protective ventilatory strategies—that are now considered best practice for mechanical ventilation in general critically ill patients—can be in conflict with brain protection. Indeed, in our study, even patients with normal intracranial pressure were ventilated maintaining normal levels of $Paco_2$, demonstrating a reluctance to use permissive ventilator strategies, although this has shown to be effective in reducing mortality in acute respiratory distress syndrome (ARDS) patients (27). In a cross-sectional study including 30,742 patients with cerebral injury admitted to ICUs in Australia and New Zealand, hypercapnic acidosis was associated with increased mortality, whereas compensated hypercapnia was not associated with an

TABLE 3.
Comparison of Complications Over the Course of Mechanical Ventilation and Outcomes

Complications and outcomes	2004 ($n = 938$)	2010 ($n = 1,574$)	2016 ($n = 1,640$)
Complications, *n* (%)			
Acute respiratory distress syndrome[a]	21 (2)	50 (3)	52 (3)
Ventilator-associated pneumonia[b]	61 (6.5)	74 (5)	30 (2)
Sepsis[c]	53 (6)	211 (13)	167 (10)
Cardiovascular failure[d]	174 (18)	510 (32)	625 (38)
Renal failure[e]	104 (11)	230 (15)	262 (16)
Hepatic failure[f]	102 (11)	69 (4)	34 (2)
Hematological failure[g]	88 (9)	77 (5)	69 (4)
Outcomes			
Days of mechanical ventilation, median (P_{25}–P_{75})[h]	6 (3–10)	6 (4–12)	5 (3–9)
Length of stay in the ICU, d, median (P_{25}–P_{75})[i]	7 (4–14)	7 (4–15)	8 (4–15)
Mortality in the ICU, *n* (%)[j]	317 (34)	484 (31)	530 (32)
Mortality at 28-d, *n* (%)[k]	340 (36)	536 (34)	512 (31)
Mortality in the hospital, *n* (%)[l]	350 (40)	581 (39)	605 (40)
Standardized mortality ratio[m]	1.09	0.97	0.93

P_{25} = 25th percentile, P_{75} = 75th percentile.

[a]$p = 0.172$ for comparison between 2004 vs 2010; $p = 0.172$ for comparison between 2004 vs 2016; and $p = 0.992$ for comparison between 2010 vs 2016.

[b]$p = 0.054$ for comparison between 2004 vs 2010; $p < 0.001$ for comparison between 2004 vs 2016 and for comparison between 2010 vs 2016.

[c]$p < 0.001$ for comparison between 2004 vs 2010 and for comparison between 2004 vs 2016; $p = 0.005$ for comparison between 2010 vs 2016.

[d]$p < 0.001$ for comparison between 2004 vs 2010 and for comparison between 2004 vs 2016; $p = 0.001$ for comparison between 2010 vs 2016.

[e]$p = 0.012$ for comparison between 2004 vs 2010; $p = 0.001$ for comparison between 2004 vs 2016; and $p = 0.283$ for comparison between 2010 vs 2016.

[f]$p < 0.001$ for all comparisons.

[g]$p < 0.001$ for comparison between 2004 vs 2010 and for comparison between 2004 vs 2016; $p = 0.352$ for comparison between 2010 vs 2016.

[h]$p = 0.530$ for comparison between 2004 vs 2010; $p = 0.259$ for comparison between 2004 vs 2016; and $p = 0.050$ for comparison between 2010 vs 2016.

[i]$p = 0.466$ for comparison between 2004 vs 2010; $p = 0.193$ for comparison between 2004 vs 2016; and $p = 0.506$ for comparison between 2010 vs 2016.

[j]$p = 0.113$ for comparison between 2004 vs 2010; $p = 0.442$ for comparison between 2004 vs 2016; and $p = 0.339$ for comparison between 2010 vs 2016.

[k]$p = 0.264$ for comparison between 2004 vs 2010; $p = 0.009$ for comparison between 2004 vs 2016; and $p = 0.087$ for comparison between 2010 vs 2016.

[l]$p = 0.652$ for comparison between 2004 vs 2010; $p = 0.958$ for comparison between 2004 vs 2016; and $p = 0.557$ for comparison between 2010 vs 2016.

[m]Standardized mortality ratio is calculated as observed hospital mortality: expected hospital mortality predicted by Simplified Acute Physiology Score II.

Missing data for status at discharge from hospital in 259 patients (58 patients in 2004, 78 patients in 2010, and 123 in 2016).

TABLE 4.
Analysis of 28-Day Mortality in Cohort From 2016

Variables	Mortality (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age, yr			
< 65	26	1 (reference)	
65–75	33	1.40 (1.05–1.85)	
≥ 75	44	2.18 (1.69–2.81)	1.80 (1.40–2.30)
Simplified Acute Physiology Score II > 50 points	43	2.88 (2.32–3.58)	2.31 (1.87–2.86)
Neurologic disease			
Intoxication/overdose	17	1 (reference)	
Brain trauma	28	1.84 (1.20–2.83)	1.80 (1.40–2.30)
Metabolic	30	2.00 (1.28–3.12)	
Hemorrhagic stroke	40	3.07 (2.03–4.63)	3.96 (2.59–6.06)
Ischemic stroke	43	3.45 (2.18–5.47)	3.94 (2.47–6.31)
Other cause	17	0.94 (0.53–1.66)	
Events within first 48 hr			
Hypercapnia			
No	30	1 (reference)	
Compensated	20	0.58 (0.35–0.98)	
Hypercapnic acidosis	36	1.30 (1.00–1.70)	
Number of organ dysfunction		1.82 (1.68–1.98)	1.79 (1.59–2.00)
0	20		
1	29		
2	42		
3	59		
4	87		
5	87		

OR = odds ratio.

increase in adverse outcome similar to patients with normocapnia and normal pH levels (22). No clear recommendations are currently available for respiratory management of patients with acute brain injury, and this may contribute to institutional or individual variations in the clinical practice, and that may ultimately result in differences in outcome (28, 29).

In general, in critically ill patients, the goals of mechanical ventilation have changed over the past years from maintaining normal blood gas values to maintaining adequate gas exchange while attempting to minimize lung injury. In fact, the use of high tidal volume and driving pressure are associated with an increased rate of ARDS and worsening outcome (30–36).

Variable	Points
Hemorrhagic stroke	2
Ischemic stroke	2
Brain trauma	1
Age > 75 years	1
SAPS II > 50 points	1
Dysfunction organ within first 48 hours*	1 point for each dysfunction (0 to 5)

** Defined as SOFA score > 2 points*

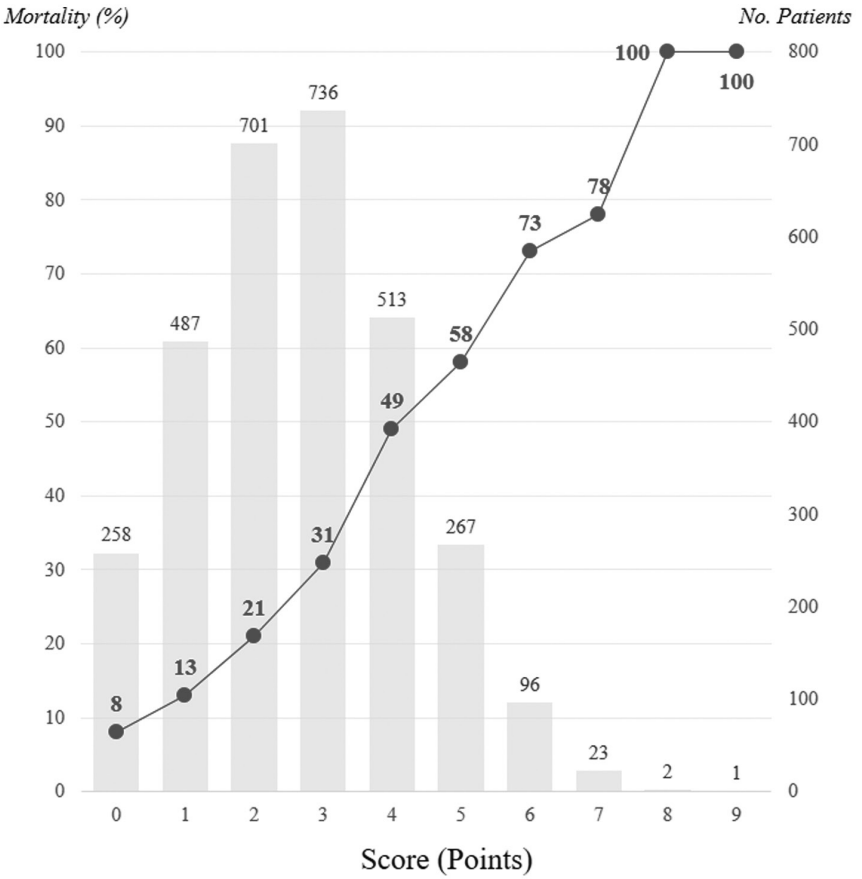

Figure 1. Predictive score for 28-d mortality and mortality according to score in 2016 cohort. SAPS II = Simplified Acute Physiology Score II, SOFA = Sequential Organ Failure Assessment.

On the basis of these results, physicians have progressively applied lower tidal volumes in the general mechanically ventilated population and particularly among those with ARDS (3, 20, 37). This trend has also been observed in the present study; in the three study periods, brain-injured patients received more often a protective lung ventilation, with lower tidal volume and higher PEEP levels, and time of ventilatory support with protective ventilation strategy was also increased.

The overall management of mechanically ventilated patients has changed over time. Volume assist-control remained the most common ventilator mode used, but its use decreased, with a higher number of patients receiving pressure-control mode ventilation in the last decade (3). Similarly, although conventional ventilatory support in severe brain-injured patients relies on the use of assist-control ventilation (1), our observational study showed a significant increase in the use of pressure support ventilation. The increased use of pressure support modes could be related to a reduced use and decrease in the depth of sedation over the last years. Current evidence in the neurocritical care settings suggests to minimize exposure to sedating agents to maximize reliability of the neurologic examination. Changes over time in weaning have also been detected in neurologic critically ill patients (1). Over the last years, a gradual reduction of ventilatory support was used more frequently than spontaneous breathing trials. These tendencies have also been reported in previous observational studies in the general population of mechanically ventilated patients (3, 20).

A previous study demonstrated that changes in mechanical ventilation practice were associated with a significant decrease in mortality over time, despite a similar proportion of patients with complications related to mechanical ventilation and organ dysfunctions (3). In contrast, two before-after studies have recently evaluated the efficacy of protective ventilation strategy in patients with brain injury. In both these studies (38, 39), the use of

protective ventilation did not alter outcome or impair intracranial pressure, provided that the level of $PaCO_2$ was monitored and maintained within normal ranges. In our mixed population of neurologic patients, we did not observe any change in the length of stay in the ICU and mortality over the years, but only a decrease in the duration of ventilatory support in the last period. This result may explain a reduction in the percentage of ventilator-associated pneumonia in recent years. Clinical practice, critically ill population, and mechanical ventilation management have dramatically changed since 2004 (20). This could explain why there are not differences in overall outcomes and in the development of ARDS, despite the use of lower tidal volumes. In addition, due to the heterogeneity of neurologic disorders, the beneficial effects of lung-protective strategies may be different according to different neuropathologic events and at different stages of the disease.

Mortality rates have not consistently decreased in patients with brain injury over the past decades (5, 6, 12, 13, 40). In contrast, substantial reductions in mortality rates for neurocritical care patients have been found when brain-injured patients were managed in dedicated neurocritical care units, using multimodal monitoring and an organized, protocol-based approach (41–45). These findings are remarkable considering that there are few interventions in neurocritical care that have demonstrated to have a beneficial effect on outcome. Therefore, another possible explanation for the absence of differences in outcomes over time in our mechanically ventilated neurologic patients could be that they were not treated in dedicated neurocritical care units. Also, the 2016 cohort had a lower mean GCS, which could explain the similar mortality.

Therefore, although we observed a reduction in tidal volume and use of moderate PEEP, this strategy alone was not associated with an improvement in survival. As shown by the results of our analysis, other factors than mechanical ventilation management may influence the mortality of brain-injured patients. Some of them, such as the etiology of neurologic disease, a low GCS score, and the severity of the disease determined with SAPS, have been previously identified in other studies with neurocritical care patients (1, 14, 16). We observed an increase of extrapulmonary organ dysfunctions such as hemodynamic and renal failure, suggesting that nonpulmonary extracranial injury could add prognostic value in the overall neurologic patient population. We therefore propose a simple score for predicting mortality at 28 days in neurologic critically ill patients requiring mechanical ventilation, which included simple parameters that easily allow the identification of patients at high risk of death.

Our study has several limitations. First, this was a post hoc analysis of previously and prospectively collected clinical data from a wide variety of ICUs, patient conditions, and clinical practices. Also, the large number of ICUs participating in the three study periods may cause heterogeneity in patients' management and treatment. However, ICU-mortality of neurologic patients was similar in all studies (34% in 2004, 31% in 2010, and 32% in 2016; $p = 0.274$). Third, we did not collect details regarding the strategies applied for the treatment of intracranial hypertension or specific monitoring data (intracranial pressure, cerebral perfusion pressure, etc.), but we assume that brain-injured patients have been treated according to the most recent protocols and guidelines. Fourth, this study focused on details related to mechanical ventilation, and we did not assess specifically neurologic outcome.

In conclusion, despite the implementation of protocols and clinical practice guidelines, mortality of neurologic patients has not improved over years. Protective mechanical ventilation has been implemented with no substantial effect on pulmonary complications or survival. We found a strong influence of several prognostic factors on mortality such as advanced age, the severity of the disease, organ dysfunctions, and the etiology of neurologic disease. Finally, this study also provides valuable information about mechanically ventilation practice in patients with neurologic disease across several countries and how clinical management has changed over the last years.

1 *Hospital Universitario de Getafe & Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain.*

2 *Department of Surgical Sciences and Integrated Diagnostics, University of Genoa & San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy.*

3 *Unidad de Bioestadística Clínica Hospital Ramón y Cajal, Instituto Ramón y Cajal de Investigaciones Sanitarias (IRYCIS) & Centro de Investigación en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain.*

4 *Servicio de Neumología, Instituto Ramón y Cajal de Investigaciones Sanitarias (IRYCIS) & Universidad de Alcalá, Madrid, Spain.*

5 *Medizinische Hochschule Hannover, Hannover, Germany.*

6 *Peking Union Medical College Hospital, Beijing, People's Republic of China.*

7 *University Hospital of Poitiers, Poitiers, France.*
8 *Hospital Nacional Alejandro Posadas, Buenos Aires, Argentina.*
9 *Clínica Medellín & Universidad Pontificia Bolivariana, Medellín, Colombia.*
10 *Interdepartmental Division of Critical Care Medicine, Toronto, ON, Canada.*
11 *Hospital Regional 1° de Octubre, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), México DF, México.*
12 *Pulmonary Research Laboratory, Federal University of Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil.*
13 *Hospital Universitario Sao Jose, Belo Horizonte, Brazil.*
14 *Hospital Universitario de Montevideo, Montevideo, Uruguay.*
15 *Università degli Studi G. d'Annunzio Chieti e Pescara, Chieti, Italy.*
16 *Department of Critical Care Medicine, Flinders University, Adelaide, SA, Australia.*
17 *Bombay Hospital Institute of Medical Sciences, Mumbai, India.*
18 *Istanbul Faculty of Medicine, Istanbul, Turkey.*
19 *Center for Clinical Epidemiology of Samsung Medical Center, Seoul, South Korea.*
20 *Hospital Fattouma Bourguina, Monastir, Tunisia.*
21 *Hospital de Especialidades Eugenio Espejo, Quito, Ecuador.*
22 *Papageorgiou Hospital, Thessaloniki, Greece.*
23 *Centre Hospitalier Universitarie Ibn Sina-Mohammed V University, Rabat, Morocco.*
24 *Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.*
25 *South Texas Veterans Health Care System and University of Texas Health, San Antonio, TX.*

This work was performed at ICU, Hospital Universitario de Getafe, Getafe, Spain.

The VENTILA Group can be found in ***Appendix 1*** *(http://links.lww.com/CCM/G193).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http:/journals.lww.com/ccmjournal).

Supported, in part, by grant from Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública, Instituto de Salud Carlos III, Madrid, Spain, and Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain.

Dr. Thille received funding from Fisher & Paykel, GE Healthcare, Maquet-Getinge, and Covidien. Dr. Amin received funding from CIPLA, Sanofi, and Fresenius. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Address requests for reprints to: Eva E. Tejerina, MD, PhD, Intensive Care Unit, Hospital Universitario de Getafe, Carretera de Toledo, km 12.5, 28905 Getafe, Spain. E-mail: evateje@gmail.com

REFERENCES

1. Pelosi P, Ferguson ND, Frutos-Vivar F, et al; Ventila Study Group: Management and outcome of mechanically ventilated neurologic patients. *Crit Care Med* 2011; 39:1482–1492
2. Esteban A, Anzueto A, Frutos F, et al; Mechanical Ventilation International Study Group: Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. *JAMA* 2002; 287:345–355
3. Esteban A, Frutos-Vivar F, Muriel A, et al: Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med* 2013; 188:220–230
4. Kramer AH, Zygun DA: Declining mortality in neurocritical care patients: A cohort study in Southern Alberta over eleven years. *Can J Anaesth* 2013; 60:966–975
5. Roozenbeek B, Maas AI, Menon DK: Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 2013; 9:231–236
6. Stein SC, Georgoff P, Meghan S, et al: 150 years of treating severe traumatic brain injury: A systematic review of progress in mortality. *J Neurotrauma* 2010; 27:1343–1353
7. van Asch CJ, Luitse MJ, Rinkel GJ, et al: Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: A systematic review and meta-analysis. *Lancet Neurol* 2010; 9:167–176
8. Nieuwkamp DJ, Setz LE, Algra A, et al: Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: A meta-analysis. *Lancet Neurol* 2009; 8:635–642
9. Feigin VL, Lawes CM, Bennett DA, et al: Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurol* 2009; 8:355–369
10. Sandvei MS, Mathiesen EB, Vatten LJ, et al: Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts, 1984-2007. *Neurology* 2011; 77:1833–1839
11. Lovelock CE, Rinkel GJ, Rothwell PM: Time trends in outcome of subarachnoid hemorrhage: Population-based study and systematic review. *Neurology* 2010; 74:1494–1501
12. Redpath C, Sambell C, Stiell I, et al: In-hospital mortality in 13,263 survivors of out-of-hospital cardiac arrest in Canada. *Am Heart J* 2010; 159:577–583.e1
13. Colantonio A, Croxford R, Farooq S, et al: Trends in hospitalization associated with traumatic brain injury in a publicly insured population, 1992-2002. *J Trauma* 2009; 66:179–183
14. Broessner G, Helbok R, Lackner P, et al: Survival and long-term functional outcome in 1,155 consecutive neurocritical care patients. *Crit Care Med* 2007; 35:2025–2030
15. Girotra S, Nallamothu BK, Spertus JA, et al; American Heart Association Get with the Guidelines–Resuscitation Investigators: Trends in survival after in-hospital cardiac arrest. *N Engl J Med* 2012; 367:1912–1920
16. Carney N, Totten AM, O'Reilly C, et al: Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017; 80:6–15

17. Mascia L, Sakr Y, Pasero D, et al; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators: Extracranial complications in patients with acute brain injury: A post-hoc analysis of the SOAP study. *Intensive Care Med* 2008; 34:720–727
18. Sutherasan Y, Vargas M, Pelosi P: Protective mechanical ventilation in the non-injured lung: Review and meta-analysis. *Crit Care* 2014; 18:211
19. Frisvold SK, Robba C, Guérin C: What respiratory targets should be recommended in patients with brain injury and respiratory failure? *Intensive Care Med* 2019; 45:683–686
20. Esteban A, Ferguson ND, Meade MO, et al; VENTILA Group: Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008; 177:170–177
21. Peñuelas O, Muriel A, Abraira V, et al: Inter-country variability over time in the mortality of mechanically ventilated patients. *Intensive Care Med* 2020; 46:444–453
22. Tiruvoipati R, Pilcher D, Botha J, et al: Association of hypercapnia and hypercapnic acidosis with clinical outcomes in mechanically ventilated patients with cerebral injury. *JAMA Neurol* 2018; 75: 818–826
23. Zygun DA, Kortbeek JB, Fick GH, et al: Non-neurologic organ dysfunction in severe traumatic brain injury. *Crit Care Med* 2005; 33:654–660
24. Ho KM, Burrell M, Rao S: Extracranial injuries are important in determining mortality of neurotrauma. *Crit Care Med* 2010; 38:1562–1568
25. Murray GD, Butcher I, McHugh GS, et al: Multivariable prognostic analysis in traumatic brain injury: Results from the IMPACT study. *J Neurotrauma* 2007; 24:329–337
26. Davis DP, Idris AH, Sise MJ, et al: Early ventilation and outcome in patients with moderate to severe traumatic brain injury. *Crit Care Med* 2006; 34:1202–1208
27. Huijben JA, Volovici V, Cnossen MC, et al; CENTER-TBI investigators and participants: Variation in general supportive and preventive intensive care management of traumatic brain injury: A survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Crit Care* 2018; 22:90
28. Cnossen MC, Polinder S, Andriessen TM, et al: Causes and consequences of treatment variation in moderate and severe traumatic brain injury: A multicenter study. *Crit Care Med* 2017; 45:660–669
29. Bulger EM, Nathens AB, Rivara FP, et al; Brain Trauma Foundation: Management of severe head injury: Institutional variations in care and effect on outcome. *Crit Care Med* 2002; 30:1870–1876
30. Elmer J, Hou P, Wilcox SR, et al: Acute respiratory distress syndrome after spontaneous intracerebral hemorrhage*. *Crit Care Med* 2013; 41:1992–2001
31. Mascia L, Zavala E, Bosma K, et al: High tidal volume is associated with the development of acute lung injury after severe brain injury: An international observational study. *Crit Care Med* 2007; 35:1815–1820
32. Gajic O, Frutos-Vivar F, Esteban A, et al: Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive Care Med* 2005; 31:922–926
33. Hoesch RE, Lin E, Young M, et al: Acute lung injury in critical neurological illness. *Crit Care Med* 2012; 40:587–593
34. Holland MC, Mackersie RC, Morabito D, et al: The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. *J Trauma* 2003; 55:106–111
35. Tejerina E, Pelosi P, Muriel A, et al; for VENTILA group: Association between ventilatory settings and development of acute respiratory distress syndrome in mechanically ventilated patients due to brain injury. *J Crit Care* 2017; 38:341–345
36. Moskowitz A, Grossestreuer AV, Berg KM, et al; Center for Resuscitation Science: The association between tidal volume and neurological outcome following in-hospital cardiac arrest. *Resuscitation* 2018; 124:106–111
37. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800
38. Asehnoune K, Mrozek S, Perrigault PF, et al; The BI-VILI study group: A multi-faceted strategy to reduce ventilation-associated mortality in brain-injured patients. The BI-VILI project: A nationwide quality improvement project. *Intensive Care Med* 2017; 43:957–970
39. Roquilly A, Cinotti R, Jaber S, et al: Implementation of an evidence-based extubation readiness bundle in 499 brain-injured patients. A before-after evaluation of a quality improvement project. *Am J Respir Crit Care Med* 2013; 188:958–966
40. Sutherasan Y, Peñuelas O, Muriel A, et al; VENTILA GROUP: Management and outcome of mechanically ventilated patients after cardiac arrest. *Crit Care* 2015; 19:215
41. Knopf L, Staff I, Gomes J, et al: Impact of a neurointensivist on outcomes in critically ill stroke patients. *Neurocrit Care* 2012; 16:63–71
42. Burns JD, Green DM, Lau H, et al: The effect of a neurocritical care service without a dedicated neuro-ICU on quality of care in intracerebral hemorrhage. *Neurocrit Care* 2013; 18:305–312
43. Damian MS, Ben-Shlomo Y, Howard R, et al: The effect of secular trends and specialist neurocritical care on mortality for patients with intracerebral haemorrhage, myasthenia gravis and Guillain-Barré syndrome admitted to critical care: An analysis of the Intensive Care National Audit & Research Centre (ICNARC) national United Kingdom database. *Intensive Care Med* 2013; 39:1405–1412
44. Kramer AH, Zygun DA: Do neurocritical care units save lives? Measuring the impact of specialized ICUs. *Neurocrit Care* 2011; 14:329–333
45. Kramer AH, Zygun DA: Neurocritical care: Why does it make a difference? *Curr Opin Crit Care* 2014; 20:174–181