Evolution of Mortality over Time in Patients Receiving Mechanical Ventilation

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***Rationale*: Baseline characteristics and management have changed over time in patients requiring mechanical ventilation; however, the impact of these changes on patient outcomes is unclear.**

***Objectives*: To estimate whether mortality in mechanically ventilated patients has changed over time.**

***Methods*: Prospective cohort studies conducted in 1998, 2004, and 2010, including patients receiving mechanical ventilation for more than 12 hours in a 1-month period, from 927 units in 40 countries. To examine effects over time on mortality in intensive care units, we performed generalized estimating equation models.**

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Baseline characteristics and management have changed over time in patients requiring mechanical ventilation; however, the impact of these changes on patient outcomes is unclear.

What This Study Adds to the Field

The implementation of mechanical ventilation has significantly changed in the last decade. These changes have likely resulted in a significant decrease in short-term mortality.

***Measurements and Main Results*: We included 18,302 patients. The reasons for initiating mechanical ventilation varied significantly among cohorts. Ventilatory management changed over time ($P <$ 0.001), with increased use of noninvasive positive-pressure ventilation (5% in 1998 to 14% in 2010), a decrease in tidal volume (mean 8.8 ml/kg actual body weight [SD = 2.1] in 1998 to 6.9 ml/kg [SD = 1.9] in 2010), and an increase in applied positive end-expiratory pressure (mean 4.2 cm H_2O [SD = 3.8] in 1998 to 7.0 cm of H_2O [SD = 3.0] in 2010). Crude mortality in the intensive care unit decreased in 2010 compared with 1998 (28 versus 31%; odds ratio, 0.87; 95% confidence interval, 0.80–0.94), despite a similar complication rate. Hospital mortality decreased similarly. After adjusting for baseline and management variables, this difference remained significant (odds ratio, 0.78; 95% confidence interval, 0.67–0.92).**

***Conclusions*: Patient characteristics and ventilation practices have changed over time, and outcomes of mechanically ventilated patients have improved.**

Clinical trials registered with www.clinicaltrials.gov (NCT01093482).

Keywords: mechanical ventilation; mortality; epidemiology; cohort study

Mechanical ventilation remains a cornerstone in the supportive management of patients with acute respiratory failure, and is one

TABLE 1. COMPARISON OF GENERAL CHARACTERISTICS OF PARTICIPATING UNITS AND BASELINE CHARACTERISTICS OF PATIENTS

	Cohort 1998	Cohort 2004	Cohort 2010	*P* Value*
Participating units, n	361	349	494	
Medical, %	19	16	17	<0.001
Medical–Surgical, %	77	68	73	
Surgical, %	4	13.5	5	
Neurological, %	—	2	1.5	
Other, %	—	0.4	3	
Number of beds, median (IQR)	10 (8, 14)	10 (8, 15)	12 (9, 19)	<0.001
Proportion of mechanically ventilated patients, %	33%	25%	35%	<0.001
Patients included, n	5,183	4,968	8,151	
Geographical area, n (%)				
Europe	2,387 (46)	2,133 (43)	3,407 (42)	<0.001
USA/Canada	1,455 (28)	1,341 (27)	929 (11)	
Latin America	1,222 (24)	1,306 (26)	1,692 (21)	
Africa	119 (2)	110 (2)	167 (2)	
Asia	0	78 (2)	1,242 (15)	
Oceania	0	0	714 (9)	
Age, mean (SD), yr	59 (17)	59 (17)	61 (17)	<0.001
Female sex, n (%)	1,985 (39)	1,967 (40)	3,105 (38)	0.23
Weight, mean (SD), kg	72 (17)	76 (20)	75 (20)	<0.001
Body mass index, mean (SD), kg/m^2	n.d.	27 (7)	27 (6.5)	0.122
Simplified Acute Physiology Score II on admission, mean (SD), points	44 (17)	42 (18)	45 (18)	<0.001
Previous tracheotomy, n (%)	102 (2)	123 (2)	180 (2)	0.22
Noninvasive ventilation at home, n (%)	73 (1)	n.d.	213 (3)	<0.001
Bilevel positive airway pressure, n (%)	38 (52)		81 (38)	
Continuous positive airway pressure, n (%)	35 (48)		132 (62%)	
Main reason for mechanical ventilation, n (%)†				
Chronic obstructive pulmonary disease	522 (10)	267 (5)	524 (6)	<0.001
Asthma	79 (2)	63 (1)	98 (1)	0.26
Other chronic pulmonary disease	60 (1)	85 (2)	142 (2)	0.019
Neurologic disease	864 (17)	938 (19)	1,574 (19)	<0.001
Metabolic, n (% of neurologic)	n.d.	129 (14)	265 (17)	
Overdose/intoxication, n (% of neurologic)	n.d.	148 (16)	211 (13)	
Hemorrhagic stroke, n (% of neurologic)	n.d.	310 (33)	470 (30)	
Ischemic stroke, n (% of neurologic)	n.d.	119 (13)	214 (13.5)	
Brain trauma, n (% of neurologic)	n.d.	228 (24)	302 (19)	
Other cause, n (% of neurologic)	n.d.	4 (0.4)	112 (7)	
Neuromuscular disease	94 (2)	58 (1)	74 (1)	<0.001
Acute respiratory failure				
Postoperative	1,080 (21)	1,053 (21)	1,750 (21)	0.68
Pneumonia	721 (14)	528 (11)	819 (10)	<0.001
Community acquired, n (% of pneumonia)	n.d.	376 (71)	539 (66)	
Hospital acquired, n (% of pneumonia)	n.d.	152 (29)	280 (34)	
Sepsis	458 (9)	449 (9)	726 (9)	0.93
Acute respiratory distress syndrome	231 (5)	148 (3)	281 (3)	<0.001
Congestive heart failure	539 (10)	285 (6)	617 (8)	<0.001
Cardiac arrest	100 (2)	239 (5)	473 (6)	<0.001
Trauma	407 (8)	284 (6)	367 (4.5)	<0.001
Aspiration	129 (3)	139 (3)	200 (2.5)	0.44
Other cause of acute respiratory failure	367 (7)	432 (9)	506 (6)	<0.001

Definition of abbreviations: IQR = interquartile range; n.d. = no data available.

* Chi-square tests were used for the comparison of categorical variables between groups; Student's *t* test and ANOVA were used for the comparison of continuous variables.

† Because of rounding, percentages may not total 100. In 1998, more than one cause of acute respiratory failure per patient was permitted.

of the defining interventions of intensive care medicine as a specialty. Basic science, translational, and physiological studies have all informed clinical trials, which, in turn, have shown significant impact in areas such as avoidance of ventilator-induced lung injury (1–5), liberation from mechanical ventilation (6–10), and improved outcomes using noninvasive positive-pressure ventilation (11, 12). Little is known, however, about the impact of these interventions on mortality in a real-world setting.

In 1998 (13) and 2004 (14), we performed two observational studies on the use of mechanical ventilation and its associated outcomes. In the first, we focused on describing mortality outcomes and identifying factors that impacted survival (13). In the second, we systematically reviewed clinical trials published in the prior 6 years and examined the implementation of this published evidence (14). The main finding of this study was the increasing use of noninvasive positive-pressure ventilation, a reduction in tidal volumes for patients with acute respiratory distress syndrome (ARDS), and more pressure support and less synchronized intermittent mandatory ventilation being used for liberation from mechanical ventilation. Despite these encouraging findings, our data failed to demonstrate a significant improvement in outcomes. Possible reasons for these results include lack of statistical power, or a true lack of outcome improvements due to differences in intensive care unit (ICU) admission patterns over time, an insufficient magnitude of practice change, or a lack of efficacy of these therapies in unselected populations outside the setting of a clinical trial.

TABLE 2. COMPARISON OF VARIABLES RELATED TO MANAGEMENT

	Cohort 1998 (*n* = *5,183*)	Cohort 2004 (*n* = *4,968*)	Cohort 2010 (*n* = *8,151*)	*P* Value*
Noninvasive positive-pressure ventilation before admission in the ICU, n (%)	n.d.	n.d.	429 (5)	—
Noninvasive positive-pressure ventilation at admission in the ICU, n (%)	256 (5)	479 (10)	1,169 (14)	<0.001
Mode of ventilation, days of use per 1,000 d of invasive mechanical ventilation (excluding days during weaning from mechanical ventilation process)				
Assist-control	627	412	330	<0.001
SIMV	66	21	34	<0.001
SIMV-PS	132	132	94	<0.001
Pressure support	65	125	237	<0.001
PCV	75	125	130	<0.001
APRV/BIPAP	n.d.	66	91	<0.001
PRVC	n.d.	98	61	<0.001
Other mode	35	21	23	<0.001
Ventilator settings over the course of invasive ventilation				
Tidal volume, mean (SD)				
ml/kg actual body weight	8.8 (2.1)	7.6 (2.1)	6.9 (1.9)	<0.001
ml/kg predicted body weight	n.d.	9.3 (2.3)	8.2 (2.0)	<0.001
Positive end-expiratory pressure, cm H_2O, mean (SD)	4.2 (3.8)	5.4 (4.6)	7.0 (3.0)	<0.001
Total respiratory rate, breaths per minute, mean (SD)	18 (11)	18 (6)	19 (6)	<0.001
Sedation, n (%)	3,164 (61)	3,486 (70)	5,755 (71)	<0.001
Analgesia, n (%)	2,241 (43)	n.d.	5,043 (62)	<0.001
Neuromuscular blocking, n (%)	686 (13)	524 (10.5)	890 (11)	<0.001
Liberation from mechanical ventilation				
Met criteria, n/eligible patients (%)†	3,640/5,008 (73)	3,005/4,682 (64)	5,111/7,323 (70)	<0.001
Scheduled extubation, n/patients met criteria (%)	2,858/3,640 (78.5)	2,714/3,005 (90)	4,151/5,111 (81)	<0.001
Unplanned extubation, n/patients at risk (%)‡	179/4,906 (4)	135/4,559 (3)	654/7,143 (9)	<0.001
Noninvasive positive-pressure ventilation after extubation, n/eligible patients (%)§	n.d.	308/2,849 (11)	473/4,805 (10)	0.17
Reintubation, n/ patients at risk (%)‖	424/3,037 (14)	319/2,849 (11)	643/4,805 (13)	0.005
After scheduled extubation	350/2,858 (12)	278/2,714 (10)	511/4,151 (12)	0.001
After unplanned extubation	74/179 (41)	41/135 (30)	132/654 (20)	<0.001
Tracheotomy, n/patients at risk (%)¶	546/4,906 (11)	664/4,559 (15)	993/7,143 (14)	<0.001
Percutaneous, n (%)	n.d.	362 (54.5)	526 (53)	0.53

Definition of abbreviations: APRV/BIPAP = airway pressure release ventilation/biphasic positive airway pressure; ICU = intensive care unit; PCV = pressure-controlled ventilation; PRVC = pressure regulated volume control; PS = pressure support; n.d. = no data available; SIMV = synchronized intermittent mandatory ventilation.

* Chi-square tests were used for the comparison of categorical variables between groups; ANOVA was used for the comparison of continuous variables.

† Eligible patients for criteria for liberation from mechanical ventilation: overall cohort excepting patients with successful noninvasive positive-pressure ventilation.

‡ Patients at risk for unplanned extubation: overall cohort excepting patients with a previous tracheotomy and patients with successful noninvasive positive-pressure ventilation.

§ Eligible patients for noninvasive positive-pressure ventilation after extubation: scheduled and unplanned extubated patients.

‖ Patients at risk for reintubation: scheduled and unplanned extubated patients.

¶ Patients at risk for tracheotomy: overall cohort excepting patients with a previous tracheotomy and patients with successful noninvasive positive-pressure ventilation.

At 6 years after the last study, we have now conducted a new international study with the primary objective of estimating whether mortality in mechanically ventilated patients has changed over time. We reasoned that combining this new study with our two prior databases would give us more statistical power to demonstrate potential improvements in survival. Furthermore, allowing more time for incorporation of previous research findings into clinical practice, and performing a multivariable analysis that accounted for potential changes in case mix over time should improve the study importance. Our secondary aims were to describe the changes in the baseline and management characteristics of ventilated patients over this 12-year period.

METHODS

Design

As in previous studies (13, 14), we conducted a prospective use review of patients receiving invasive mechanical ventilation for at least 12 hours or noninvasive positive-pressure ventilation for at least 1 hour during a 1-month period starting in March 2010. National coordinators recruited local investigators (*see* full list of Investigators in the Third International Study on Mechanical Ventilation (2010) at the end of this article for 2010 and the online supplement for 2004 and 1998) from eligible ICUs (*see* Table E1 in the online supplement). Only the investigator and research coordinators at each site were aware of the exact purpose and timing of the study to minimize practice changes in response to observation. The research ethics board of each participating institution approved the protocol and waived the need for informed consent.

Protocol

We collected baseline characteristics, and daily ventilator, gas exchange, clinical management, and complications data while patients were ventilated or until Day 28. Patients were followed in hospital for mortality and length-of-stay outcomes.

For this analysis, we combined these 2010 data with those from our studies in 1998 and 2004 (13, 14). Detailed descriptions of the variables collected in each study, along with their definitions, are shown in Tables E2 and E3. One notable variable not collected in 1998 was height; we therefore express tidal volume as ml/kg actual body weight for comparisons across all three studies.

Statistical Analysis

Data are expressed as mean (±SD), median (interquartile range), and absolute and relative frequencies, as appropriate. ANOVA or Kruskal-Wallis tests were used to compare continuous variables, and Chi-square tests were used for categorical variables. We rejected the null hypothesis of no difference among cohorts at a nominal significance level of

0.05. These analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL).

To estimate the effect of the year of study on ICU mortality, we used generalized estimating equation models with a binomial distribution and logit link function to measure the impact of time (by cohort year), accounting for the effects related to the clustering of patients receiving care from the same ICU (15). For the purpose of the analysis, the overall population of patients from the three studies (n = 18,302) was randomly divided into two sets: *modeling group* (n = 13,644) and *validation group* (n = 4,658). A first generalized estimating equation estimative model was derived entering the following variables: year of study (reference year, 1998), geographical area (Europe, USA–Canada, Latin American, Africa, Asia, and Oceania), age, sex, ICU characteristics (type of unit [medical, surgical, medical–surgical, neurological, other] and size of the unit [fewer than 10 beds, 10–20 beds, more than 20 beds]), severity at ICU admission (Simplified Acute Physiology Score II), and reason for mechanical ventilation. We built on this model by entering daily variables related to management over the course of ventilation: type of ventilation (invasive or noninvasive), inspired fraction of oxygen, positive end-expiratory pressure (PEEP), tidal volume (ml/kg actual body weight), prone position (yes/no), minute ventilation, use of continuous intravenous sedatives (yes/no), and use of neuromuscular blockers (yes/no). These two models were then evaluated for consistency of effects in the validation set. As a sensitivity analysis, we ran these models in the cohort of patients included from ICUs that participated in all three studies. These analyses were performed using Stata Software 11.0 (StataCorp LP, College Station, Texas).

RESULTS

Characteristics of Participating ICUs and Included Patients

The characteristics of the 927 participating ICUs and 18,302 patients across the studies are shown in Table 1. These include 2,913 patients from 55 ICUs that participated in all three studies. Further details regarding the ICU distribution by country across studies are shown in Table E4.

Management during Mechanical Ventilation

Variables related to management in the ICU are shown in Table 2. The use of noninvasive positive-pressure ventilation increased significantly over the 12-year period: 5% in 1998, 10% in 2004, and 14% in 2010 ($P < 0.001$). Meanwhile, the median duration of noninvasive positive-pressure ventilation decreased over time (3 d [interquartile range, 2–6] in 1998 versus 2 d [interquartile range, 2–4] in 2004 and 2 d [interquartile range, 1–3] in 2010; $P < 0.001$). The need for intubation among these patients was not higher in 2010: 32% in 1998, 40% in 2004, and 29% in 2010 ($P < 0.001$).

During invasive ventilation, volume-cycled assist-control ventilation remained the most common ventilator mode, but its use has decreased over time in favor of other modes, particularly pressure support (Table 2; *see* also Figure E1). Among all patients, we observed a significant decrease in tidal volume and an increase in PEEP ($P < 0.001$) (Table 2).

In the subgroup of patients with ARDS, tidal volume (expressed as ml/kg actual body weight) was also significantly ($P < 0.001$) reduced over time (Figure 1). The proportion of patients receiving a ventilation strategy with pressure/volume limitation (arbitrarily defined as tidal volume below 6 ml/kg actual body weight; or tidal volume below 8 ml/kg actual body weight and plateau or peak inspiratory pressure less than 30 cm H_2O [13]) increased significantly over time: 29% in 1998, 57% in 2004, and 67.5% in 2010 ($P < 0.001$). In addition, PEEP levels increased significantly ($P < 0.001$; Figure 2). The use of adjunctive therapies, such as prone positioning, was infrequent, and remained stable: 9% in 1998, 5% in 2004, and 7% in 2010 ($P = 0.07$).

A process of weaning or liberation from mechanical ventilation began in 73% of patients in 1998, 64% in 2004, and 70% in 2010 (Table 2). The proportion of patients who successfully completed their first attempt of liberation from mechanical ventilation increased over time (49% in 1998, 55% in 2004, and 63.5% in 2010; $P < 0.001$). Among patients who failed their first attempt at weaning, there was a significant increase in the subsequent use of pressure support as the weaning mode, with a concomitant significant reduction in the use of synchronized intermittent mandatory ventilation with or without pressure support (Table E5). The duration of weaning in these patients, although statistically different ($P < 0.001$), was not clinically different among the three time periods (median, 3 [interquartile range, 2–5] d in 1998, 3 [interquartile range, 2–4] d in 2004, and 3 [interquartile range, 2–5] d in 2010).

The rate of reintubation after scheduled extubation remained similar over time, at around 12% (Table 2). This occurred most commonly within the first 12 hours after extubation (63% of reintubations in 1998, 57% in 2004, and 52% in 2010; $P = 0.01$).

More tracheotomies were performed in 2004 (15%) and 2010 (14%) than in 1998 (11%) ($P < 0.001$). Median time to tracheotomy from intubation, however, remained stable (12 [interquartile range, 7–17] d in 1998, 9 [interquartile range, 6–14] d in 2004, and 11 [interquartile range, 6–16] d in 2010 ($P = 0.73$).

Outcomes

A comparison of patient outcomes across the studies is shown in Table 3. Half of the patients included had at least one complication over the course of mechanical ventilation (50% in 1998,

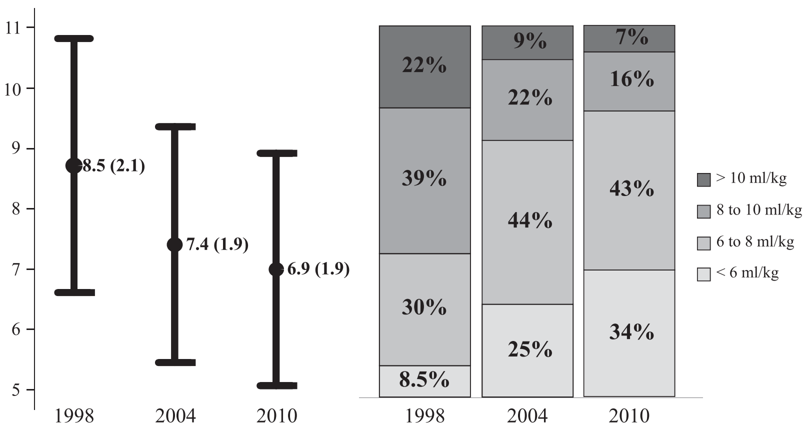

Figure 1. Evolution of the set tidal volume (ml/kg actual body weight) in patients with criteria of acute respiratory distress syndrome (ARDS). *Left*: mean (±SD); $P < 0.001$ for all comparisons with ANOVA test. *Right*: proportion of the time of mechanical ventilation in each category of tidal volume; $P < 0.001$ for all comparisons with chi-square test.

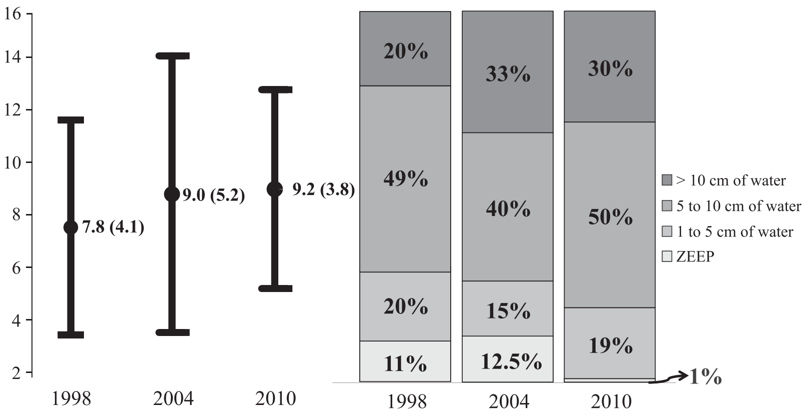

Figure 2. Evolution of the applied positive end-expiratory pressure (PEEP; cm H_2O) in patients with criteria of acute respiratory distress syndrome (ARDS). *Left*: mean (±SD); $P < 0.001$ for comparisons, with ANOVA, between 1998 versus 2004 and 1998 versus 2010; $P = 0.05$ for comparison, with ANOVA, between 2004 and 2010. *Right*: proportion of the time of mechanical ventilation ventilated in each category of PEEP. $P < 0.001$ for all comparisons with chi-square test. ZEEP = zero positive end-expiratory pressure.

48% in 2004, and 54% in 2010; $P < 0.001$). We note higher rates of sepsis and cardiovascular failure in 2010, and a reduction over time in ventilator-associated pneumonia. We observed significant differences in the duration of ventilatory support, ICU, and hospital length of stay.

Analysis of Mortality in the ICU

There was a decline in the crude ICU mortality, from 31% in 1998 to 28% in 2010 (odds ratio, 0.87; 95% confidence interval, 0.80–0.94; $P < 0.001$).

After adjustment for baseline variables, mortality in 2010 remained lower than in 1998 (odds ratio, 0.74; 95% confidence interval, 0.66–0.84; Table 4). This result was similar after management variables were added to the model (odds ratio, 0.78; 95% confidence interval, 0.67–0.92). These results were quantitatively similar in the *validation group* (final model odds ratio, 0.86; 95% confidence interval, 0.67–1.09; Table 4).

The observed mortality in the 2,913 patients from ICUs that participated in all three studies showed a similar trend: 34% in 1998, 34% in 2004, and 27% in 2010 ($P = 0.002$). Sensitivity analysis of the final model showed robust results in this subgroup, with a final adjusted odds ratio for 2010 ICU mortality of 0.58 (95% confidence interval, 0.45–0.75) relative to 1998.

DISCUSSION

Our analysis of these international multicenter studies suggests that, in mechanically ventilated patients, short-term mortality has decreased over time. Although many factors may have contributed to these results, several factors related to mechanical ventilation management may have contributed, including reducing the need for invasive mechanical ventilation, and improving both mechanical ventilation safety and the process of liberation from mechanical ventilation. This study confirms our previous work showing that changes in mechanical ventilation practices continue to follow findings of positive clinical trials, and shows, for the first time, a significant association with reduced mortality.

We have observed a significant change of mortality over time after adjustment for case mix and for variables related to ventilatory settings. Despite a similar proportion of patients with complications related to mechanical ventilation and organ dysfunctions, the intensive care mortality in 2010 was lower than in previous studies. The most likely explanation is that the overall management of mechanically ventilated patients has improved over the last 12 years. The implementation of different integrated management strategies for precipitating conditions, such as sepsis (16), protocols related to ventilator management, including sedation (10, 17, 18), and incorporating bundles of care to prevent

TABLE 3. COMPARISON OF EVENTS EMERGING OVER THE COURSE OF MECHANICAL VENTILATION AND IN THE OUTCOMES

	Cohort 1998 (*n* = 5,183)	Cohort 2004 (*n* = 4,968)	Cohort 2010 (*n* = 8,151)	*P* Value*
Events emerging over the course of mechanical ventilation				
Acute respiratory distress syndrome, n (%)	218 (4)	279 (6)	495 (6)	<0.001
Acquired ICU pneumonia, n (%)	438 (8.5)	265 (5)	359 (4)	<0.001
Sepsis, n (%)	457 (9)	400 (8)	1,473 (18)	<0.001
Barotrauma, n (%)	154 (3)	157 (3)	140 (2)	<0.001
Cardiovascular failure, n (%)	1,145 (22)	1,193 (24)	3,145 (39)	<0.001
Renal failure, n (%)	971 (19)	948 (19)	1,775 (22)	<0.001
Hepatic failure, n (%)	326 (6)	691 (14)	555 (7)	<0.001
Hematological failure, n (%)	552 (11)	795 (16)	662 (8)	<0.001
Outcomes				
Duration of ventilatory support†, median (IQR), days	4 (2, 8)	6 (3, 11)	5 (3, 10)	<0.001
Length of stay in the ICU, median (IQR), days	7 (4, 14)	8 (4, 15)	7 (4, 14)	<0.001
Length of stay in the hospital‡, median (IQR) days	16 (9,29)	17 (9,31)	17 (9,31)	0.002
Mortality, n (% [95% confidence interval])				
In the ICU	1,590 (31 [29–32])	1,533 (31 [29–32])	2,269 (28 [27–29])	<0.001
At Day 28 after admission in the ICU	1,719 (33 [32–34])	1,605 (32 [31–34])	2,445 (30 [29–31])	<0.001
In the hospital‡	1,876 (40 [38–41])	1,759 (37 [36–38])	2,733 (35 [34–36])	<0.001

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range.

* Chi-square tests were used for the comparison of categorical variables between groups; ANOVA or Kruskall-Wallis test was used for the comparison of continuous variables.

† Including duration of liberation from mechanical ventilation in the extubated patients.

‡ Patients whose date and status at discharge from hospital was unknown were not included in the calculation (465 patients in 1998, 211 patients in 2004, and 377 patients in 2010).

TABLE 4. ESTIMATION OF RELATION OF YEAR OF STUDY TO MORTALITY IN THE INTENSIVE CARE UNIT

Study Year	Modeling Group (*n* = *13,644*)	Validation Group (*n* = *4,658*)
Crude odds ratio		
1998	1	1
2004	1.01 (0.90–1.13)	1.00 (0.82–1.20)
2010	0.83 (0.75–0.93)	0.90 (0.75–1.07)
After adjustment for ICU and baseline variables		
1998	1	1
2004	1.01 (0.89–1.15)	1.05 (0.90–1.24)
2010	0.74 (0.66–0.84)	0.78 (0.67–0.92)
After adjustment for ICU and baseline variables and for daily management variables		
1998	1	1
2004	1.05 (0.90–1.24)	1.06 (0.83–1.34)
2010	0.78 (0.67–0.92)	0.86 (0.67–1.09)

Definition of abbreviation: ICU = intensive care unit.
Data presented are odds ratios (95% confidence intervals).

nosocomial infections (19, 20) could all possibly contribute to these findings.

Throughout our studies, we observed a significant decrease in delivered tidal volume, both in the general mechanically ventilated population and particularly among those with ARDS. This lung-protective strategy has been evaluated in several randomized clinical trials (1, 2, 21–23), the largest of which showed reduced mortality when tidal volume and plateau pressure were controlled in patients with acute lung injury (2). These data suggest that routine implementation of a pressure–volume limited ventilation strategy in clinical practice could reduce mortality in these patients. In a recent observational ARDS study (24), adherence to lung-protective ventilation was associated with a 3% decrease in the mortality risk at 2 years (hazard ratio, 0.97; 95% confidence interval, 0.95–0.99; $P = 0.002$). These results, like ours, suggest that these clinical trial results are robust even applied to a less selective population, as in usual clinical practice. There are also suggestions that lung-protective strategies may be important in patients who do not yet have ARDS (25–28). The fact that the odds ratio for mortality moved closer to 1 in all datasets after accounting for management variables, including tidal volume, is in keeping with the hypothesis that lung-protective ventilation is a key intervention across a broad range of mechanically ventilated patients, not just those with ARDS.

PEEP is another essential component of the ventilatory strategy in patients with ARDS. From the first report of this syndrome (29), it has been observed that PEEP can improve oxygenation by keeping recruited alveoli open and decreasing intrapulmonary shunt (30). In addition, PEEP-induced lung recruitment can decrease alveolar overdistention, because the volume of each subsequent tidal breath is shared by more open alveoli. PEEP may also decrease repetitive alveolar opening and closing during the respiratory cycle, thereby preventing lung injury (31). Observational studies have reported an independent association between zero PEEP and mortality (32) in a heterogeneous cohort of patients who were mechanically ventilated and between low values of PEEP and mortality in patients with ARDS (33). An individual patient data meta-analysis (3, 4) from randomized trials (1, 34–38) comparing higher versus lower PEEP levels while controlling tidal volume in patients with acute lung injury overall showed no statistically significant difference in hospital mortality (random effects model relative risk, 0.85; 95% confidence interval, 0.71–1.01). However, in patients with moderate to severe ARDS (39), higher levels of PEEP were associated with a significant 4% absolute mortality reduction (40). In our analysis, we observed a marked reduction in the use of zero end-expiratory pressure and a significant increase in the use of higher PEEP, especially in patients with ARDS. Nevertheless, the mean PEEP level used in the first week of ventilatory support in 2010 (9.3 ± 3.3 cm H_2O) was still lower than that set in the higher PEEP groups of some randomized clinical trials.

The use of noninvasive positive-pressure ventilation at ICU admission has almost doubled every 6 years. This finding is similar to that reported by Chandra and colleagues (41), who observed a 46% increase in noninvasive positive-pressure ventilation use and a 42% decline in invasive mechanical ventilation use between 1998 and 2008 in patients with exacerbations of chronic obstructive pulmonary disease. Encouragingly, despite this increased use, the proportion of patients intubated after failing a trial of noninvasive positive-pressure ventilation has remained stable over time. An important observation is that patients who required invasive ventilation after noninvasive positive-pressure ventilation had higher mortality than patients who were directly intubated. This finding was described previously by our group (13, 14, 42) and others (43), and has several possible explanations. First, failure of noninvasive positive-pressure ventilation could identify patients who are difficult to ventilate or who have a higher severity of illness. In our study, patients who failed noninvasive positive-pressure ventilation had significantly higher Simplified Acute Physiology Score II scores (mean = 42) than successful patients (mean = 37), but they had lower scores than patients invasively ventilated from the beginning (mean = 45). Another explanation is that failing noninvasive ventilation is, in itself, harmful, and that delayed recognition of failure may exacerbate this harm (41).

Our study has several limitations. This is an analysis of prospectively collected clinical data from a wide variety of ICUs, patient conditions, and clinical practices, some of which are related to outcome (43). We have performed an analysis accounting for clustering by the ICUs, and we have included ICU type and size in the model to try to minimize the possible bias related to those variables. Although we used multivariable modeling, unmeasured confounders may remain, which could have impacted our results. We constructed an estimative model to evaluate the decreasing ICU mortality in the last 12 years, and we have outlined plausible explanations for this. This model has been validated and adjusted, and the results appear consistent. However, it is not possible to make a causal inference model from our observational data. In addition, we have no information about withdrawal and/or withholding of life support and its possible impact on our results. Another limitation is that we did not have all the same ICUs participating in all three studies. To some extent, this was unavoidable due to closure of some previously participating hospitals, changes in resources available for data collection at participating centers, and our goal to expand the generalizability of results by including ICUs from more countries.

In conclusion, our analysis shows that the implementation of mechanical ventilation has significantly changed in the last decade; we speculate that these changes have resulted in the significant decrease in short-term mortality.

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