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Do ventilatory parameters influence outcome in patients with severe acute respiratory infection? Secondary analysis of an international, multicentre14-day inception cohort study

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ABSTRACT

Purpose: To investigate the possible association between ventilatory settings on the first day of invasive mechanical ventilation (IMV) and mortality in patients admitted to the intensive care unit (ICU) with severe acute respiratory infection (SARI).

Materials and methods: In this pre-planned sub-study of a prospective, multicentre observational study, 441 patients with SARI who received controlled IMV during the ICU stay were included in the analysis.

Results: ICU and hospital mortality rates were 23.1 and 28.1%, respectively. In multivariable analysis, tidal volume and respiratory rate on the first day of IMV were not associated with an increased risk of death; however, higher driving pressure (DP: odds ratio (OR) 1.05; 95% confidence interval (CI): 1.01–1.1, $p = 0.011$), plateau pressure (Pplat) (OR 1.08; 95% CI: 1.04–1.13, $p < 0.001$) and positive end-expiratory pressure (PEEP) (OR 1.13; 95% CI: 1.03–1.24, $p = 0.006$) were independently associated with in-hospital mortality. In subgroup analysis, in hypoxemic patients and in patients with acute respiratory distress syndrome (ARDS), higher DP, Pplat, and PEEP were associated with increased risk of in-hospital death.

Conclusions: In patients with SARI receiving IMV, higher DP, Pplat and PEEP, and not tidal volume, were associated with a higher risk of in-hospital death, especially in those with hypoxemia or ARDS.

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; COPD, Chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DP, driving pressure; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; IC GLOSSARI, Intensive Care Global Study on Severe Acute Respiratory Infection; ICU, Intensive Care Unit; IQR, interquartile ranges; IMV, invasive mechanical ventilation; LOS, length of stay; NYHA, New York Heart Association.; OR, odds ratio; PBW, predicted body weight; PCV, pressure-controlled ventilation; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; RCT, randomized controlled trial; SAPS, Simplified Acute Physiology Score; SARI, severe acute respiratory infection; SD, standard deviation; SIMV, Synchronized intermittent mandatory ventilation; SOFA, Sequential Organ Failure Assessment; VCV, volume-controlled ventilation; VILI, ventilator induced lung injury; Vt, tidal volume.

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1. Introduction

Mechanical ventilation has been recognized as a possible cause of lung damage [1,2]. The initial injury to the lung parenchyma is mechanical and leads to a non-physiological distortion of the extracellular matrix of the lung [3], activating a biological inflammatory response and promoting so-called "ventilator induced lung injury (VILI)" [1]. The benefits and harms of mechanical ventilation depend not only on the adjustment of ventilatory parameters, such as tidal volume (Vt), positive end-expiratory pressure (PEEP), respiratory rate, and inspiratory airflow, but also on the interpretation of ventilator-derived parameters, such as peak (Ppeak), plateau (Pplat) and driving pressures, which may be useful to guide ventilatory strategies [4].

To minimize VILI, a lung-protective ventilation strategy is recommended in patients with acute respiratory distress syndrome (ARDS) [5-10]. However, even when receiving lung protective ventilation, patients with ARDS may remain exposed to forces that can induce VILI [11-13]. In an analysis of individual data from 3562 patients with ARDS enrolled in nine randomized controlled trials (RCTs), Amato et al. showed that driving pressure, calculated as the difference between Pplat and PEEP, was the variable that correlated best with survival [14]. A large observational study showed that patients with moderate and severe ARDS had increased hospital mortality if the driving pressure was >14 cmH_2O [15]. The possible impact of driving pressure on outcome in patients without ARDS is still uncertain [13].

Severe acute respiratory infection (SARI), defined by the World Health Organization as an acute respiratory illness of recent onset (within 7 days) that includes fever (≥38 °C), cough, and dyspnoea, is a common cause of admission to the intensive care unit (ICU) and is associated with considerable morbidity and high mortality rates [16]. Invasive mechanical ventilation (IMV) is frequently required in these patients; however, the impact of ventilator settings on outcomes has not been investigated.

In this sub-study of the Intensive Care Global Study on Severe Acute Respiratory Infection (IC GLOSSARI) [16], we investigated the possible association between ventilatory settings on the first day of ventilation and mortality in critically ill patients admitted to the ICU with SARI. Our hypothesis was that ventilator settings would have an impact on outcome in patients with SARI, especially those with higher disease severity.

2. Methods

This study was a pre-planned analysis of the IC-GLOSSARI, a prospective, multicentre, 14-day inception cohort study. Participation was voluntary, with no financial incentive. Institutional review board approval was obtained by the participating institutions according to local ethical regulations. Informed consent was not obtained due to the observational and anonymous nature of data collection. A list of contributing centers is provided in the Appendix 1.

Full details of study design and data collection have been reported elsewhere [16] and are briefly described in Box 1 in the Supplementary material. Patients were followed up for vital status in-hospital until ICU discharge, death, or for a maximum of 60 days, whichever occurred first.

In this sub-study, we included only patients with SARI who received controlled IMV during the ICU stay, defined as ventilation through an artificial airway (endotracheal or tracheostomy tube) using controlled modes of mechanical ventilation (excluding continuous positive airway pressure (CPAP), pressure support, or spontaneous breathing).

2.1. Data collection

Data were collected using a secure internet-based platform. Admission parameters included demographics, comorbid diseases, clinical and laboratory data to calculate the Simplified Acute Physiology Score (SAPS) II [17], and ventilatory parameters. Organ function was evaluated daily using the Sequential Organ Failure Assessment (SOFA) score [18]. After the day of admission, ventilatory parameters were recorded daily in the morning at a standard time for each ICU (6:00–8:00 AM).Daily data collection was continued for 28 days following admission to the ICU or until ICU discharge or death. Further details are presented in Box 1 of the Supplementary material.

2.2. Definitions

Infection was defined according to the definitions of the International Sepsis Forum [19]. Organ failure was defined as a SOFA score > 2 for the organ in question. Hospital-acquired SARI was defined as the development of SARI 48 h or more after hospital admission [20]. Patients with healthcare-related SARI were defined according to the criteria listed in Box 1 of the Supplementary material. Patients were classified as having community-acquired SARI if they did not fit the criteria for healthcare-related or hospital-acquired SARI. ARDS was defined according to the Berlin definitions [21].

We calculated driving pressure as the difference between Pplat and PEEP. In the absence of Pplat, Ppeak was used. The predicted body weight in kg of male patients was calculated as equal to 50 + 0.91 (height in centimeters – 152.4) and that of female patients as equal to 45.5 + 0.91 (height in centimeters – 152.4) [5].

2.3. Outcome parameters

The primary outcome parameter was in-hospital mortality within 60 days of admission to the ICU. Secondary outcome parameters included death in the ICU, lengths of stay (LOS) in the ICU and hospital, and organ failure as assessed by the SOFA score.

2.4. Statistical analysis

Data were analyzed using IBM® SPSS® Statistics software, version 22 for Windows. The Kolmogorov–Smirnov test was used to verify the normality assumption of continuous variables. Difference testing between groups was performed using Student's *t*-test, Mann–Whitney test, Chi-square test, or Fisher's exact test, as appropriate.

To evaluate the possible association between ventilatory parameters and outcome, we performed a multivariable logistic regression analysis with in-hospital death as the dependent variable. Covariates to be included in the final models were determined from a univariate logistic regression analysis ($p < 0.2$) of demographic variables (age and sex), comorbid conditions, adequacy of initial antibiotics, severity scores on admission to the ICU (SAPS II and SOFA scores), severity of respiratory failure according to the PaO_2/FiO_2 ratio on the first day of mechanical ventilation, Vt and respiratory rate. Collinearity between variables was ruled out before covariates were introduced in the model. Goodness of fit was tested using a Hosmer and Lemeshow test, and odds ratios (OR) with 95% confidence interval (CI) were computed. Because driving pressure, Pplat, Ppeak, and PEEP are mathematically linked and were confirmed to be collinear ($R^2 > 0.6$, variance inflation factor > 5, pairwise), we constructed separate logistic regression models for each parameter including the previously mentioned parameters. The multivariable models were also adjusted for geographic region.

To further explore the effect of driving pressure, Pplat, and PEEP on outcome, multivariable logistic regression analyses were performed with in-hospital death as the dependent variable within subgroups of patients classified according to the median value of driving pressure, Pplat, PEEP, Vt, PaO_2/FiO_2, and the presence or not of ARDS on the first day of mechanical ventilation. Covariates considered for these analyses were SAPS II score, age, and the degree of hypoxia as assessed by the PaO_2/FiO_2 ratio. Driving pressure, Pplat, and PEEP were included separately in the multivariable models for each subgroup due to multicollinearity.

Data are presented as means with standard deviation, medians, and interquartile ranges (IQR), or counts and percentages (*n*, %). All statistics were two-tailed and a *p* value <0.05 was considered significant.

3. Results

A total of 206 ICUs from 42 countries, mostly in Western Europe, contributed to the study. Of 663 patients admitted with SARI, 369 (55.7%) required controlled IMV on the day of admission to the ICU and 72 (10.8%) required controlled IMV later during the ICU stay (Table S1, Supplementary material). Other respiratory support therapies are shown in Table S1 of the Supplementary material.

3.1. Characteristics of the study group

The characteristics of patients with SARI requiring controlled IMV at any time during the ICU stay ($n = 441$) are shown in Table 1. The mean SAPSII and SOFA scores on admission to the ICU were 53.7 (SD: 18.8) and 7.4 (SD: 4.3), respectively. Pneumonia was most commonly community acquired (66.1%). Baseline characteristics and outcomes of the patients varied across geographical areas (Table S2, Supplementary material). On ICU admission, 27.6% ($n = 119$) of the patients had ARDS. Severe ARDS occurred in 20.9% of patients ($n = 90$) at some time during the ICU stay. The most prevalent mode on the first day of ventilation was pressure-controlled ventilation (PCV; $n = 187$ [42.4%]). Prone positioning was used in 17 (3.9%) patients, inhaled nitric oxide in 10 (2.3%) and extracorporeal membrane oxygenation (ECMO) in 4 (0.9%) (Table S3, Supplementary material). Ventilatory settings are shown in Table S3 of the Supplementary material. The distribution of Pplat according to Vt is shown in Figure S1in the Supplementary material and was similar in patients with and without ARDS on the first day of controlled IMV.

3.2. Morbidity and mortality

Overall ICU and hospital mortality rates were 23.1 and 28.1%, respectively. The median ICU and hospital LOS were 7 (3–14) and 14 (7–25) days, respectively. The most common non-respiratory organ failures on admission or at any time during the ICU stay were cardiovascular and renal failure (Table S4, Supplementary material).

Non-survivors ($n = 124$) were older than survivors, had greater SAPS II and SOFA scores on admission to the ICU, were more frequently male, and were more likely to have cancer, be immunosuppressed, and have received inadequate initial antibiotics (Table 1). Non-respiratory organ failure and severe ARDS were more common during the ICU stay in non-survivors than in survivors (Table S4, Supplementary material). Hospital LOS was longer in survivors than in non-survivors (17 [9-28] vs. 8 [2–17.5] days, $p < 0.001$).

3.3. Ventilatory parameters and outcome

On the first day of IMV, non-survivors received higher levels of FiO_2 and PEEP, and had higher respiratory rates than survivors (Table S3, Supplementary material). Vt values were similar in survivors and non-survivors. Airway pressures on the first day of mechanical ventilation were higher in non-survivors than survivors. ICU and hospital mortality

Table 1
Basic characteristics of patients with severe acute respiratory infection (SARI) requiring controlled invasive mechanical ventilation, according to in-hospital survival status.

	All patients ($n = 441$)	Alive ($n = 297$)	Dead ($n = 124$)	*p* value
Age, years, mean ± SD	62.9 ± 16.2	61.5 ± 16.3	66.9 ± 15	0.001
Male, n (%)	260 (59.1)	165 (55.6)	83 (67.5)	0.024
SAPS II, mean ± SD	53.7 ± 18.8	49.8 ± 15.9	64.18 ± 20.8	<0.001
SOFA score, mean ± SD	7.4 ± 4.3	6.6 ± 3.8	9.5 ± 4.6	<0.001
Acquisition of pneumonia, n(%)				0.570
Community-acquired	290 (66.1)	201 (68.1)	78 (62.9)	
Healthcare-related	58 (13.2)	37 (12.5)	19 (15.3)	
Hospital-acquired	91 (20.7)	57 (19.3)	27 (21.8)	
Comorbid conditions, n(%)				
Smoking	196 (44.4)	134 (45.1)	52 (41.9)	0.549
COPD	126 (28.6)	92 (31.0)	30 (24.2)	0.162
Diabetes mellitus	123 (27.9)	85 (28.6)	31 (25)	0.449
Insulin dependent	45 (10.2)	34 (11.4)	11 (8.9)	0.435
Non-insulin dependent	78 (17.7)	51 (17.2)	20 (16.1)	0.795
Congestive heart failure	76 (17.2)	47 (15.8)	22 (17.7)	0.628
NYHA I-II	47 (10.7)	32 (10.8)	11 (8.9)	0.557
NYHA III-IV	29 (6.6)	15 (5.1)	11 (8.9)	0.138
Coronary heart disease	74 (16.8)	47 (15.8)	22 (17.7)	0.628
Chronic renal failure	64 (14.5)	36 (12.1)	24 (19.4)	0.053
With dialysis	17 (3.9)	11 (3.7)	6 (4.8)	0.590
Without dialysis	47 (10.7)	25 (8.4)	18 (14.5)	0.060
Liver disease	19 (4.3)	11 (3.7)	6 (4.8)	0.590
Asthma	30 (6.8)	25 (8.4)	4 (3.2)	0.055
Cancer	62 (14.1)	35 (11.8)	25 (20.2)	<0.001
Metastatic	17 (3.9)	7 (2.4)	10 (8.1)	0.007
Non metastatic	45 (10.2)	28 (9.4)	15 (12.1)	0.410
Hematologic cancer	30 (6.8)	7 (2.4)	21 (16.9)	<0.001
Immunosuppression	56 (12.7)	27 (9.1)	26 (21.0)	0.001
Cerebrovascular disease	51 (11.6)	31 (10.4)	16 (12.9)	0.464
Chemotherapy	34 (7.7)	14 (4.7)	18 (14.5)	0.001
Previous corticosteroid use	95 (21.5)	58 (19.5)	36 (29.0)	0.033
HIV	6 (1.4)	3 (1.0)	3 (2.4)	0.698
Alcohol abuse	51 (11.6)	38 (12.8)	9 (7.3)	0.100
Antibiotic adequacy, n (%)	327 (74.1)	234 (78.8)	81 (65.3)	0.004

Missing values: Age:1, Sex:1, acquisition of pneumonia:2.
COPD: Chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; SAPS: Simplified Acute Physiology Score; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; NYHA: New York Heart Association.

rates increased with higher quartiles of Ppeak and Pplat and were higher in patients who required PEEP >7cmH_2O or driving pressures ≥22 cmH_2O (Fig. S2, Supplementary material). ICU and hospital mortality rates were similar across quartiles of Vt (Fig. S3, Supplementary material). The PaO_2/FiO_2 ratio was lower and PCO_2 higher in non-survivors than in survivors (Table S3, Supplementary material).

3.4. Multivariable and subgroup analyses

In the multivariable analyses with in-hospital death as the dependent variable, older age, higher SAPS II and SOFA scores on admission to the ICU, hematologic malignancy, and immunosuppression were independently associated with an increased risk of in-hospital death (Table 2). Adequate initial antibiotics and greaterPaO_2/FiO_2 ratio were independently associated with a lower risk of in-hospital death. Vt and respiratory rate were not associated with the risk of in-hospital death in these patients; however, higher driving pressure, Pplat, Ppeak and PEEP were independently associated with in-hospital death.

On the first day of controlled IMV, driving pressure was independently associated with a higher risk of in-hospital death in patients with high Pplat (>21 cmH_2O), high PEEP (>7 cmH_2O), and high Vt (>8.9 ml/kg) (Fig. 1). Pplat was independently associated with a higher risk of in-hospital death for all levels of Vt and driving pressure (Fig. 2). High PEEP levels were associated with a higher risk of in-hospital death in patients with high driving pressure, high Pplat, low Vt, and irrespective of the presence of ARDS (Fig. 3).

In subgroup analysis, higher driving pressure, Pplat, and PEEP were associated with a higher risk of in-hospital death in hypoxemic patients (PaO_2/FiO_2 ratio ≤ median value of 228) and in patients with ARDS (Figs. 1-3).

Table 2
Summary of logistic regression analysis with in-hospital death as the dependent variable*.

	Odds ratio(95%CI)	*p* value
Age, per year	1.03 (1.01–1.05)	0.004
Sex, female	0.62 (0.33–1.16)	0.142
SAPS II, per point	1.02 (1.01–1.04)	0.001
SOFA score, per point	1.10 1.03–1.18	0.003
Comorbid conditions		
COPD	0.70 (0.35–1.39)	0.315
NYHA III – IV	1.27 (0.38–4.25)	0.694
CRF –without dialysis	2.28 (0.94–5.53)	0.066
Metastatic cancer	1.29 (0.35–4.69)	0.693
Asthma	0.12 (0.01–1.05)	0.056
Hematologic cancer	8.17 (1.89–35.30)	0.005
Immunosuppression	2.46 (1.07–5.63)	0.033
Alcohol abuse	0.64 (0.24–1.69)	0.374
Adequacy of initial antibiotics	0.32 (0.17–0.62)	0.001
ARDS on admission†		
Mild ARDS	2.43 (0.70–8.43)	0.161
Moderate ARDS	0.46 (0.17–1.20)	0.115
Severe ARDS	1.33 (0.51–3.48)	0.557
Ventilatory settings on the first day of invasive mechanical ventilation		
Respiratory rate, per 1 bpm	1.00 (0.97–1.02)	0.985
Tidal volume, per 1 ml/kg	0.90 (0.79–1.04)	0.109
Driving pressure, per 1 cmH_2O‡	1.05 (1.01–1.09)	0.011
PEEP, per 1 cmH_2O‡	1.13 (1.03–1.24)	0.006
Peak pressure, per 1 cmH_2O‡	1.05 (1.01–1.10)	0.004
Plateau pressure, per 1 cmH_2O‡	1.08 (1.04–1.13)	<0.001
PaO_2/FiO_2 ratio, per 1 mmHg	0.99 (0.98–0.99)	0.005

SAPS II: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure.
† With No-ARDS as the reference category.
‡ Introduced alternately in different multivariable models due to collinearity.
* Adjusted for geographic region. Covariate inclusion in the final models was based on a univariate logistic regression analysis ($p < 0.2$) within the categories demographic variables (age and sex), comorbid conditions, adequacy of initial antibiotics, severity of respiratory failure according to the PaO_2/FiO_2 ratio on the first day of mechanical ventilation, in addition to tidal volume and respiratory rate. The displayed values refer to those considered in the model which includes the driving pressure as a covariate (Hosmer & Lemeshow goodness of fit Chi square: 4.28, $p = 0.831$; Nagelkerke's $R^2 = 0.449$). Changes in the pressure parameters (‡) did not influence the significant *p* values of the other covariates. Patients who were excluded from the multivariable analysis due to missing variables ($n = 162$) had similar severity of respiratory failure as assessed by the PaO_2/FiO_2 ratio on the first day of mechanical ventilation and similar mortality rates compared to those who were included in the analysis.

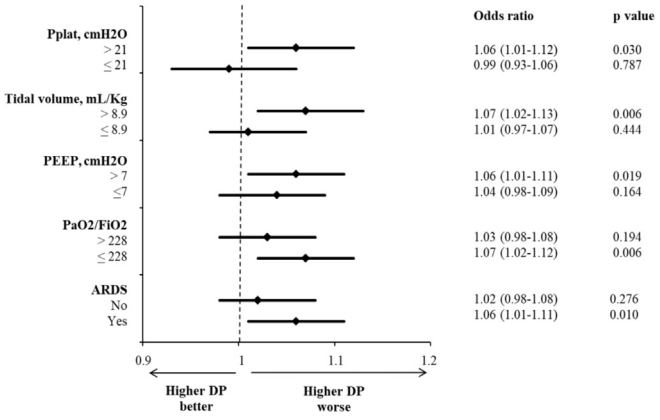

Fig. 1. Adjusted odds ratio of in-hospital death per 1 cmH_2O increase in driving pressure (DP) within subgroups of patients classified according to the median value of plateau pressure (Pplat), positive end-expiratory pressure (PEEP), tidal volume, PaO2/FiO2, and the presence or absence of acute respiratory distress syndrome (ARDS) on the first day of mechanical ventilation. Adjustment was made for simplified acute physiology score (SAPS II) score, age, and the degree of hypoxemia as assessed by the PaO_2/FiO_2 ratio.

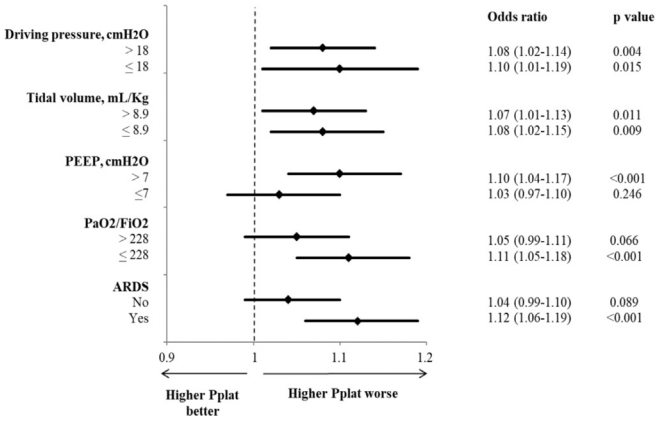

Fig. 2. Adjusted odds ratio of in-hospital death per 1 cmH_2O increase in plateau pressure within subgroups of patients classified according to the median value of driving pressure, positive end-expiratory pressure (PEEP), tidal volume, PaO2/FiO2, and the presence or absence of acute respiratory distress syndrome (ARDS) on the first day of mechanical ventilation. Adjustment was made for simplified acute physiology score (SAPS II) score, age, and the degree of hypoxia as assessed by the PaO_2/FiO_2 ratio.

4. Discussion

The main findings of our study were that in patients with SARI who required controlled IMV in the ICU,1) higher pressures on the first day of mechanical ventilation but not Vt were independently associated with in-hospital death;2) the impact of driving pressure was confirmed only in patients with high airway pressures (Pplat and PEEP) and those with high Vt; 3) Pplat was independently associated with an increased risk of in-hospital death irrespective of Vt and driving pressure and in patients with high PEEP levels; and 4) in hypoxemic patients and patients with ARDS, higher driving pressure, Pplat, and PEEP were associated with an increased risk of in-hospital death.

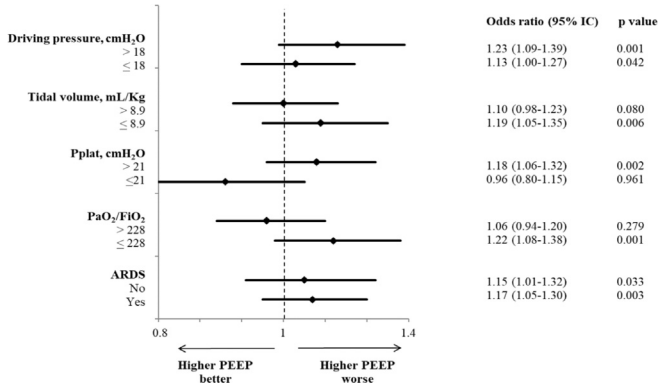

Fig. 3. Adjusted odds ratio of in-hospital death per 1 cmH_2O increase in positive end-expiratory pressure (PEEP) within subgroups of patients classified according to the median value of driving pressure, plateau pressure (Pplat), tidal volume, PaO_2/FiO_2, and the presence or absence of acute respiratory distress syndrome (ARDS) on the first day of mechanical ventilation. Adjustment was made for simplified acute physiology score (SAPS II) score, age, and the degree of hypoxia as assessed by the PaO_2/FiO_2 ratio.

In our cohort, higher Vt was not associated with mortality. Interestingly, low Vts were not adopted in these patients on the first day of mechanical ventilation. The lack of a relationship between Vt and outcome may be explained by the low range of Vts in our study, with a median of about 8.9 ml/kg, suggesting adoption of a Vt mostly less than 10 ml/kg in the patients enrolled. The relatively low airway pressures in these patients may also have outweighed the possible deleterious effects of high Vt. Indeed, high-volume ventilation has been reported to increase the risk of permeability pulmonary edema even in previously non-injured lung as well as increased formation of edema in the injured lung [22] and may provoke initiation of a pro-inflammatory cascade, which then results in lung injury. [23] Since the ARMA RCT, it is clear that high Vt can contribute to the development of lung injury. [5] In addition, two meta-analyses reported that the number of patients breathing without assistance by day 28 was higher in patients ventilated with Vt of 6 ml/kg predicted body weight (PBW) compared to those ventilated with Vt of 10 ml/kg; lower Vt values were also associated with a reduced risk of pulmonary complications. [8,10] Therefore, lower Vts, perhaps targeted to airway pressures, may be safer in patients with SARI.

Higher airway pressures were independently associated with in-hospital mortality, especially in hypoxemic patients and those with ARDS. Indeed, current guidelines recommend limiting Pplat to 30 cmH_2O in septic patients with ARDS. [24] However, the guidelines also suggest limiting Pplat to 20 cmH_2O in patients with normal lung function in the ICU or undergoing major abdominal surgery with a high risk of complications. As a surrogate for lung stress, [1] Pplat is the most commonly used clinical variable to indicate lung overdistention. [4] A meta-analysis demonstrated a significant correlation between Pplat>35cmH_2O and the risk of barotrauma. [25] In a retrospective analysis of septic patients with acute respiratory failure, Pplat on the first day of ICU admission was predictive of outcome, with lower values being associated with lower mortality rates. [26] More recently, a large prospective observational study suggested that higher Pplat was a potentially modifiable factor associated with increased in-hospital mortality in critically ill patients without ARDS. [27]

In our study, higher PEEP levels were associated with worse outcome. Although high PEEP may decrease refractory hypoxemia in patients with ARDS, it also increases static strain on the lung, which may be harmful, especially in those with lower degrees of lung recruitability. [28] We assume that high PEEP levels were used in the more severe cases in our study, and a confounding effect of severity of illness cannot be excluded. The confounding effect of the associated higher Pplat levels may also explain, at least in part, the observed worse outcome in patients with higher PEEP levels. It has also been shown that the percentage of recruitable lung tissue is extremely variable. [29] Therefore, assessment of individual recruitability may be essential to individualize PEEP settings and better determine the optimal PEEP level. Nonetheless, the benefit of higher PEEP levels remains controversial in patients with and without ARDS. A large RCT comparing high versus low levels of PEEP with similar Vts during intraoperative ventilation, found that higher levels of PEEP were not associated with a reduced risk of postoperative pulmonary complications. [30] A systematic review and meta-analysis reported that treatment with higher levels of PEEP was associated with improved hospital survival but only in patients with ARDS. [31]

The deleterious effects of higher driving pressure were confirmed only in patients with high airway pressures (Pplat and PEEP) and high Vt, as well as in hypoxemic patients and patients with ARDS. Driving pressure is directly related to stress forces in the lung and adjusting Vt by targeting driving pressure, rather than ideal body weight, maybe lung-protective in patients with more severe lung injury and low end-expiratory lung volumes [11,13]. In a secondary analysis of RCTs of mechanical ventilation in ARDS patients, Amato et al. showed that driving pressure was the variable most strongly associated with mortality [14]. In an observational study of 2377 patients, driving pressure > 14 cmH_2O was associated with an increased risk of hospital mortality in patients with moderate and severe ARDS [15]. Schmidt et al. also reported that the driving pressure was associated with risk of death in hypoxemic patients with a PaO_2/FiO_2 ratio < 300 regardless of the results of the chest radiograph or the presence of ARDS [32].

The lack of association between driving pressure and risk of death in patients with SARI who did not have ARDS or hypoxemia may be related to the low degree of preexisting lung damage. Our results are consistent with those of a recent cohort study of 622 mechanically ventilated adult patients without ARDS [32]. Nonetheless, in a secondary analysis of a study on mechanically ventilated patients without ARDS in the emergency department, Fuller et al. reported that driving pressure was a risk factor for mortality and the later development of ARDS [33]. A meta-analysis of individual patient data from 17 clinical trials including 2250 patients who received protective ventilation during general anaesthesia for surgery suggested that driving pressure was associated with the occurrence of postoperative pulmonary complications [34]. We can speculate that our cohort was underpowered to detect a potentially harmful effect of driving pressure in this subgroup of patients or that the relatively lower driving pressures applied in these patients were within the safe limits that are not associated with worse outcome.

Our study has several limitations. First, the multivariable analysis is limited to the variables included in this analysis, so that the possible confounding effect of unmeasured variables, such as use of recruitment manoeuvres, cannot be excluded. Furthermore, the mathematical link and collinearity between the various airway pressures precludes the inclusion of these parameters in the same multivariable model. Second, the number of patients in the subgroup analyses is too small to allow for adjustment for a large number of covariates; nonetheless, we adjusted for severity of illness and the degree of hypoxemia within these subgroups. Third, ventilator parameters were recorded at a fixed time point and may have been subject to changes during the day. Fourth, multivariate adjustment may not necessarily imply causality and the possible impact of the underlying pathologic alterations in the lung tissue on outcome may not be completely excluded. Indeed, the lower PaO_2/FiO_2 ratio and higher $PaCO_2$ values in non-survivors signify marked impairment of lung mechanics and function in these patients. Finally, due to the observational nature of the study, the influence of spontaneous breathing cannot be completely excluded and may have confounded measurements of airway pressures.

5. Conclusion

In patients with SARI who required controlled IMV in the ICU, higher airway pressures but not Vt were independently associated with in-

hospital mortality. In hypoxemic patients and in patients with ARDS, higher driving pressure, Pplat, and PEEP were associated with an increased risk of in-hospital death.

Ethics approval and consent to participate

Institutional review board approval was obtained by the participating institutions according to local ethical regulations. Informed consent was not obtained due to the observational and anonymous nature of data collection.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YS, TM, JA, RF, and LB designed the study. YS, JSV, PRB, MO, TP, TS, KZ, SAÑ-S, TP, RF, FST, FvH. contributed to data collection and study coordination, YS, TM, and JA handled the data and performed the analysis. YS, TM, JA, and LB wrote the first draft of the manuscript. All the authors reviewed, revised, and approved the submitted manuscript. All authors have complete access to data and hold responsibility for integrity and correctness of data.

Declarations of interest

YS and MO are section editors in the Journal of Critical Care. The remaining authors declare that they have no conflicts of interest.

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We acknowledge the investigators at our participating centres, listed in the Appendix.

Appendix 1. List of participating centres by region & country in alphabetical order

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The trials group of the European Society of Intensive Care (ESICM): (G Francois)

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Denmark: Holbaek Sygehus, Holbaek (R Medici); Rigshopitalet, Copenhagen (J Nielsen); Glostrup Sygehus, Glostrup (A Bendtsen, H Siegel)

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Georgia: Georgian Critical Care Medicine Institute, Tbilissi (Z Kheladze)

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Vietnam

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Appendix 2. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.08.008.

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