Eur Respir J 2013; 41: 157–164
DOI: 10.1183/09031936.00221611

Effectiveness of an inspiratory pressure-limited approach to mechanical ventilation in septic patients

Ignacio Martin-Loeches*, Candelaria de Haro*, R. Phillip Dellinger#, Ricard Ferrer¶, Gary S. Phillips+, Mitchell M. Levy§ and Antonio Artigas*

ABSTRACT: Severe sepsis is one of the most common causes of acute lung injury (ALI) and is associated with high mortality. The aim of the study was to see whether a protective strategy based approach with a plateau pressure <30 cmH_2O was associated with lower mortality in septic patients with ALI in the Surviving Sepsis Campaign international database.

A retrospective analysis of an international multicentric database of 15,022 septic patients from 165 intensive care units was used.

Septic patients with ALI and mechanical ventilation (n=1,738) had more accompanying organ dysfunction and a higher mortality rate (48.3% *versus* 33.0%, p<0.001) than septic patients without ALI (n=13,284). In patients with ALI and mechanical ventilation, the use of inspiratory plateau pressures maintained at <30 cmH_2O was associated with lower mortality by Chi-squared test (46.4% *versus* 55.1%, p<0.001) and by Kaplan–Meier and log-rank test (p<0.001). In a multivariable random-effects Cox regression, plateau pressure <30 cmH_2O was significantly associated with lower mortality (hazard ratio 0.84, 95% CI 0.72–0.99; p=0.038).

ALI in sepsis was associated with higher mortality, especially when an inspiratory pressure-limited mechanical ventilation approach was not implemented.

KEYWORDS: Acute lung injury, acute respiratory distress syndrome, mechanical ventilation, sepsis

Acute lung injury (ALI) is linked to multiple causes [1]. The highest incidence of ALI occurrs in patients with sepsis [2] and sepsis-associated ALI carries the highest mortality rates [3]. The exact incidence today has not been reported after the worldwide implementation of lung-protective strategies [4]. Death usually results from multisystem organ rather than lung failure alone and patients who develop sepsis-associated ALI have a worse outcome than those without sepsis [5].

Over the past two decades, several studies have reported better outcome in patients with ALI/ARDS, based on lung-protective ventilation using low tidal volumes and pressure limitation being one of the biggest advances in the application of mechanical ventilation [4, 6]. Yet, studies continue to demonstrate low adoption of these lung protective ventilation strategies. The Surviving Sepsis Campaign (SSC) developed a quality improvement programme for the bedside management of severely septic and septic shock patients that included achieving inspiratory plateau pressures maintained at <30 cmH_2O for mechanically ventilated patients [7].

The aim of the present study was an epidemiological analysis of the impact of ALI in a large cohort of patients with sepsis, and the effect of mechanical ventilation if inspiratory plateau pressures maintained at <30 cmH_2O were associated with better outcomes in patients with and without ALI.

MATERIAL AND METHODS

Study design

We conducted a retrospective analysis from a multicentric study of a cohort of 1,738 mechanically ventilated patients with ALI of a total of 15,022 septic patients from 165 intensive care units (ICUs). The analysis set was constructed from the subjects entered into the SSC database from its launch in January 2005 to March 2008. The *a priori* data analysis plan limited inclusion to sites with ⩾20 subjects and ⩾3 months of subject enrolment. The analysis presented here was limited to the first 2 yrs of subjects at each site.

AFFILIATIONS
*Critical Care Centre, Corporación Sanitaria Universitaria Parc Tauli, Sabadell University Hospital, Universidad Autónoma de Barcelona, CIBER Enfermedades Respiratorias, Sabadell, and
¶Critical Care Dept, Mutua Terrassa University Hospital, University of Barcelona, Terrasa, Spain.
#Division of Critical Care Medicine, Dept of Medicine, Cooper University Hospital, Camden, NJ,
+Ohio State University Center for Biostatistics, Ohio State University Medical Center, Columbus, OH, and
§Division of Pulmonary, Critical Care and Sleep Medicine, Warren Alpert Medical School, Brown University, Providence, RI, USA.

CORRESPONDENCE
I. Martin-Loeches
Critical Care Center
Parc Taulí Hospital-Sabadell
Parc Tauli s/n
08208 Sabadell
Spain
E-mail: mailto:drmartinloeches@gmail.com

Received:
Dec 16 2011
Accepted after revision:
April 02 2012
First published online:
April 20 2012

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

Hospitals contributed data for a mean duration of 15.6 months (median 14 months). Subjects were characterised by baseline severe sepsis information: sepsis admission source (emergency department, ICU or ward); site of infection (pulmonary, urinary tract, abdominal, central nervous system, skin, bone, wound, catheter, cardiac, device or other); and acute organ dysfunction (cardiovascular, pulmonary, renal, hepatic or haematological). Data were entered into the SSC database locally at individual hospitals into pre-established, unmodifiable fields documenting performance data and the time of specific actions and findings. Data on the local database contained private health information (PHI) that enabled individual sites to audit and review local practice and compliance as well as provide feedback to clinicians involved in the initiative. Data stripped of PHI were submitted every 30 days to the secure master SSC server at the Society of Critical Care Medicine (Mount Prospect, IL, USA). Further details of this observational study can be found elsewhere [7].

Data collection and definitions

To be enrolled, a subject had to have a suspected site of infection, and meet two or more systemic inflammatory response syndrome criteria [8] and one or more organ dysfunction criteria. Clinical and demographic characteristics and time of presentation with severe sepsis criteria were collected for analysis of time-based measures. Patient clinical characteristics, compliance with the quality indicators, use of a protective mechanical ventilation strategy based approach (defined as plateau pressure <30 cmH_2O) and hospital mortality was analysed in patients with and without ALI.

ALI was defined as an arterial oxygen tension (P_{a,O_2})/inspiratory oxygen fraction (F_{I,O_2}) ratio <300 mmHg with

TABLE 1 Clinical characteristics of patients with or without acute lung injury (ALI)

Clinical characteristics	Other patients[#]	Patients with ALI and mechanical ventilation	p-value[¶]
Patients n (%)	13284 (88.4)	1738 (11.6)	
Mortality	33.0	48.3	<0.001
Patient location at sepsis diagnosis			
Emergency department	54.3	38.1	<0.001
Ward	34.5	37.2	
ICU	11.2	24.7	
Source of infection			
Pneumonia	41.5	66.7	<0.001
Abdominal	21.1	21.4	0.830
UTI	22.4	8.7	<0.001
Skin	6.2	3.2	<0.001
Bone	1.3	0.9	0.158
Wound	4.0	2.4	0.001
Catheter	4.2	2.8	0.004
Meningitis	1.6	1.4	0.512
Endocarditis	1.1	1.1	0.926
Device	1.1	1.0	0.572
Other infection	13.5	6.2	<0.001
Lactate variables			
Obtained on admission	83.9	76.4	<0.001
Elevated	24.9	22.0	0.009
Lactate mmol·L^{-1}	2.8 (1.6–4.6)	2.6 (1.5–4.5)	0.016[+]
Lactate >2 mmol·L^{-1} in <6 h	48.1	38.9	<0.001
Lactate >4 mmol·L^{-1} in <6 h	22.5	18.6	<0.001
Shock attributable to lactate only	5.9	1.7	<0.001
Lactate >2 mmol·L^{-1} at any time	55.1	46.1	<0.001
Lactate >4 mmol·L^{-1} at any time	25.5	21.2	<0.001
Baseline acute organ dysfunction			
Cardiovascular	85.4	87.3	0.035
Pulmonary	21.8	100.00	<0.001
Renal	37.9	51.3	<0.001
Hepatic	9.4	16.5	<0.001
Haematological	24.2	37.5	<0.001

Data are presented as % or median (interquartile range), unless otherwise stated. ICU: intensive care unit; UTI: urinary tract infection. [#]: patients with no ALI and no mechanical ventilation, ALI and no mechanical ventilation, and mechanical ventilation and no ALI; [¶]: Pearson's Chi-squared test; [+]: Wilcoxon rank-sum test.

bilateral infiltrates plus mechanical ventilation. The worst $P_{a,O_2}/F_{I,O_2}$ at the time of diagnosis of severe sepsis, entry into the database and median plateau pressure during the first 24 h after ICU admission were recorded. When a patient was included in the study and mechanically ventilated, the inspiratory plateau pressures maintained at <30 cmH_2O had to be accomplished as soon as possible and scored over the first 24 h. If a patient was not ventilated at the time of admission but was eventually ventilated, the inspiratory plateau pressure was maintained at <30 cmH_2O in the first 24 h. Quality indicators were divided into two sets of performance measures: a resuscitation bundle to be accomplished within 6 h of presentation with severe sepsis and/or septic shock, and a second set, the management bundle, to be accomplished within 24 h.

Statistical analysis

Summary statistics of patient clinical characteristics are presented as percentages for categorical variables and medians with their associated interquartile ranges for continuous variables. Pearson's Chi-squared test was used to test differences in categorical variables and the Wilcoxon rank-sum was used to test differences for continuous variables. Pearson's Chi-squared test was used to test differences between the groups for the 12 key quality indicators. The log-rank test was used to compare hospital survival curves between patients who maintained a mechanically ventilated plateau pressure of <30 cmH_2O and those who did not. A random-effects Cox proportional hazard regression (shared gamma frailty model) was used to estimate the hazard of death for those with a plateau pressure <30 cmH_2O compared with those whose pressure was $\geqslant$30 cmH_2O for patients with ALI who were mechanically ventilated. Random-effects regression is used due to the hierarchical nature of the data. Subjects were nested within specific ICUs; thus, the within-ICU and between-ICU variability were used to estimate the standard errors that were used to test the model coefficients. Both the unadjusted results and the adjusted results are presented. A risk factor modelling approach was used to determine which covariates were to be included in the model. Only covariates that acted either as a confounder or as an effect modifier were included. The following covariates were evaluated: region (North America, Europe or South America); sepsis admission source (emergency department, ward or ICU); infection location (urinary tract infection, abdominal, meningitis, skin, bone, wound, catheter, endocarditis, device or other); broad-spectrum antibiotic treatment; fluids; vasopressor use; drotrecogin alfa administration within 24 h; and steroids within 24 h. The method of fractional polynomials was used to determine whether the continuous variables were linear in the log hazard. The proportional hazard assumption was checked in the final Cox model. All analyses were performed using Stata 10.1 (Stata Corporation, College Station, TX, USA).

RESULTS

A total of 15,022 septic patients were included in the SSC database. From these, 7,877 were mechanically ventilated and ALI was present in 1,738 (22.1%) patients.

In patients who presented with ALI and mechanical ventilation (ALI/MV), the most frequent source of infection was pneumonia; episodes of sepsis were more frequently identified in patients admitted in the ICU than the emergency department. Patients from the ICU suffered a significantly higher number of organ failures than patients from the ward and emergency department (mean$\pm$SD 2.02$\pm$1.04, 1.99$\pm$1.04 and 1.89$\pm$0.97, respectively; $p<0.001$). Table 1 shows that patients who developed ALI/MV presented with a subsequent organ dysfunction to sepsis more frequently when compared with the rest of the patients. Patients who developed ALI/MV had a significantly higher mortality than those who did not (48.3% *versus* 33.0%, $p<0.001$) (fig. 1). When only the 7,877 patients under mechanical ventilation were compared, mortality remained different in patients with or without ALI (48.3% *versus* 45.7%, $p=0.054$).

Table 2 illustrates that of the 1,738 patients with ALI/MV, 390 (22.4%) patients did not receive a protective mechanical ventilation strategy based approach (*i.e.* their plateau pressure was $\geqslant$30 cmH_2O). Patients with a nonprotective mechanical ventilation strategy had a higher mortality (55.1% *versus* 46.4%, $p=0.0021$) (fig. 1). No significant differences were observed between patients in term of severity manifested by the number of organ failures mean (2.92 *versus* 2.93 for plateau pressure $\geqslant$30 and <30 cmH_2O, respectively; $p=0.910$).

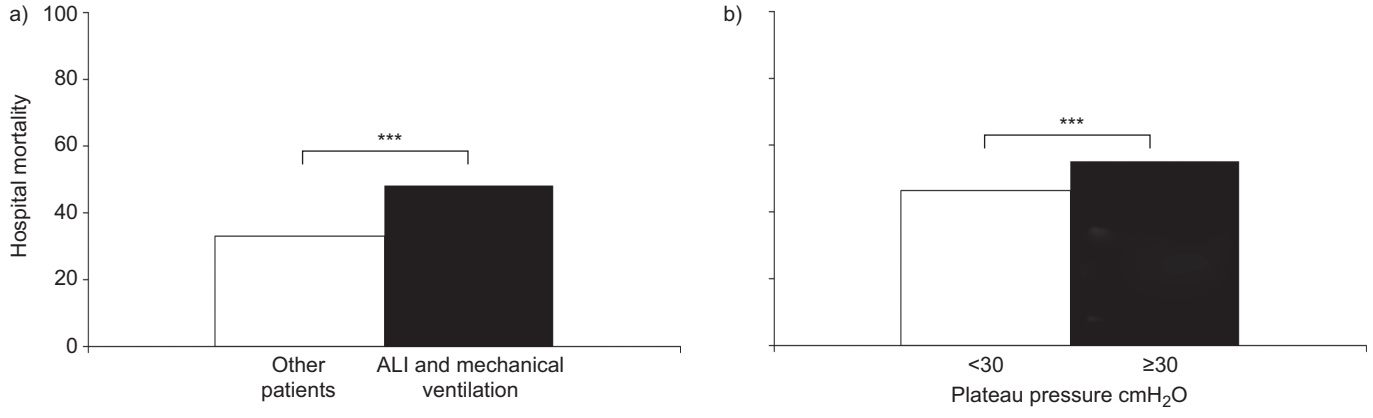

FIGURE 1. a) Hospital mortality for patients with acute lung injury (ALI) and mechanical ventilation *versus* the rest of the cohort. b) Hospital mortality based on the effect of the protective strategy in mechanically ventilated ALI patients. Patients under mechanical ventilation, n=15,022; patients with ALI, n=1,738. ***: $p<0.001$.

TABLE 2 Clinical characteristics of acute lung injury patients with mechanical ventilation by plateau pressure

Clinical characteristics	Plateau pressure cmH_2O		p-value#
	⩾30	<30	
Patients n (%)	390 (22.4)	1348 (77.6)	
Mortality	55.1	46.4	0.002
Patient location at sepsis diagnosis			
Emergency department	30.3	40.4	<0.001
Ward	36.4	37.4	
ICU	33.3	22.3	
Source of infection			
Pneumonia	68.7	66.1	0.334
Abdominal	20.0	21.7	0.461
UTI	8.0	8.9	0.556
Skin	3.9	3.0	0.428
Bone	0.3	1.0	0.141
Wound	2.8	2.2	0.495
Catheter	3.9	2.5	0.138
Meningitis	1.0	1.5	0.495
Endocarditis	1.3	1.0	0.684
Device	1.3	0.9	0.489
Other infection	5.4	6.5	0.441
Lactate variables			
Obtained on admission	76.7	76.3	0.892
Elevated	22.1	22.0	0.994
Lactate $mmol \cdot L^{-1}$	2.6 (1.3–4.4)	2.6 (1.5–4.5)	0.475¶
Lactate >2 $mmol \cdot L^{-1}$ in <6 h	36.2	39.7	0.207
Lactate >4 $mmol \cdot L^{-1}$ in <6 h	18.0	18.8	0.714
Shock attributable to lactate only	1.3	1.8	0.499
Lactate >2 $mmol \cdot L^{-1}$ at any time	44.4	46.7	0.422
Lactate >4 $mmol \cdot L^{-1}$ at any time	20.5	21.4	0.717
Baseline acute organ dysfunction			
Cardiovascular	87.4	87.2	0.919
Pulmonary	100.00	100.00	
Renal	49.5	51.8	0.425
Hepatic	15.9	16.7	0.710
Haematological	39.2	37.0	0.427

Data are presented as % or median (interquartile range), unless otherwise stated. ICU: intensive care unit; UTI: urinary tract infection. #: Pearson's Chi-squared test; ¶: Wilcoxon rank-sum test.

Tables 3 and 4 present the description of SSC quality indicators of the mechanically ventilated patients with and without ALI. Median inspiratory plateau pressure <30 cmH_2O over the first 24 h after presentation was significantly associated with survival in the ALI and non-ALI populations (p=0.010 and p<0.001, respectively).

The effect of a protected strategy (plateau pressure <30 cmH_2O) in mechanical ventilation was assessed over time from ICU admission. A survival benefit trend was observed using a Kaplan–Meier hospital survival curve (fig. 2) with a log-rank p-value of 0.075. When the results were adjusted for confounding factors (region, sepsis admission source, drotrecogin alfa administered within 24 h, vasopressor use and site quarter) using a random-effects Cox proportional hazard regression model, the survival benefit of protective mechanical ventilation strategy was significant (hazard ratio (HR) 0.84, 95% CI 0.72–0.99; p=0.038) (table 5). In addition, the same beneficial effect was noted in a cohort of patients who were mechanically ventilated but did not have ALI (HR 0.77, 95% CI 0.70–0.85; p<0.001) (table 6).

DISCUSSION

The main finding of the present study was that the presence of ALI was associated with an increased mortality in mechanically ventilated septic patients whereas a protective strategy based approach using a plateau pressure <30 cmH_2O was associated with an increased survival not only in patients with ALI but also in those who were mechanically ventilated but did not have ALI.

The Severe Sepsis Bundles based on the recommendations published by the SSC in 2004 [9] and consistent with the revised publication in 2008 [10] were designed in a manageable

TABLE 3 Description of quality indicators of acute lung injury with mechanical ventilation by survival status

Quality indicator	Survival status		p-value[+]
	Alive[#]	Died[¶]	
1) Serum lactate obtained within 6 h of presentation	63.7	62.6	0.641
2) Blood cultures collected before broad-spectrum antibiotic administration	67.0	61.4	0.015
3) Broad-spectrum antibiotic administered with 3 h of ED admission or 1 h of non-ED admission	63.6	60.5	0.182
4) For hypotension or lactate >4 mmol·L^{-1}, 20 mg·kg^{-1} crystalloid fluid bolus delivered followed by vasopressors if needed to maintain MAP ⩾65 mmHg	66.2	62.8	0.154
5) For septic shock or lactate >4 mmol·L^{-1}, central venous pressure of ⩾8 mmHg achieved within 6 h of presentation	40.5	37.2	0.196
6) For septic shock or lactate >4 mmol·L^{-1}, S_{cv,O_2} 70% (or S_{v,O_2} 65%) achieved within 6 h of presentation	18.2	14.7	0.076
7) Compliance with all applicable elements of sepsis resuscitation bundle	13.9	10.5	0.029
8) Low-dose steroids administered in accordance with standardised ICU policy within 24 h of presentation	65.5	63.7	0.495
9) Drotrecogin alfa administered in accordance with standardised ICU policy within 24 h of presentation	53.5	53.6	0.963
10) Glucose control maintained above the lower limit of normal with median <150 mg·dL^{-1} (8.3 mmol·L^{-1}) 6–24 h after presentation	53.7	45.7	0.001
11) Median inspiratory plateau pressure <30 cmH_2O over first 24 h after presentation	81.8	76.8	0.010
12) Compliance with all applicable elements of sepsis management bundle	19.3	14.9	0.015

Data are presented as %, unless otherwise stated. ED: emergency department; MAP: mean arterial pressure; S_{cv,O_2}: central venous oxygen saturation; S_{v,O_2}: mixed venous oxygen saturation; ICU: intensive care unit. [#]: n=898; [¶]: n=840; [+]: Pearson's Chi-squared test.

TABLE 4 Description of quality indicators of patients with mechanical ventilation and without acute lung injury by survival status

Quality indicator	Survival Status		p-value[+]
	Alive[#]	Died[¶]	
1) Serum lactate obtained within 6 h of presentation	74.3	71.7	0.021
2) Blood cultures collected before broad-spectrum antibiotic administration	73.6	69.3	<0.001
3) Broad-spectrum antibiotic administered with 3 h of ED admission or 1 h of non-ED admission	66.6	62.8	0.002
4) For hypotension or lactate >4 mmol·L^{-1}, 20 mg·kg^{-1} crystalloid fluid bolus delivered followed by vasopressors if needed to maintain MAP ⩾65 mmHg	75.7	72.7	0.012
5) For septic shock or lactate >4 mmol·L^{-1}, central venous pressure of ⩾8 mmHg achieved within 6 h of presentation	39.9	40.4	0.738
6) For septic shock or lactate >4 mmol·L^{-1}, S_{cv,O_2} 70% (or S_{v,O_2} 65%) achieved within 6 h of presentation	26.5	24.2	0.065
7) Compliance with all applicable elements of sepsis resuscitation bundle	20.5	15.4	<0.001
8) Low-dose steroids administered in accordance with standardised ICU policy within 24 h of presentation	70.8	67.6	0.017
9) Drotrecogin alfa administered in accordance with standardised ICU policy within 24 h of presentation	51.4	52.8	0.283
10) Glucose control maintained above the lower limit of normal with median <150 mg·dL^{-1} (8.3 mmol·L^{-1}) 6–24 h after presentation	54.8	47.6	<0.001
11) Median inspiratory plateau pressure <30 cmH_2O over first 24 h after presentation	85.8	79.9	<0.001
12) Compliance with all applicable elements of sepsis management bundle	23.5	18.1	<0.001

Data are presented as %, unless otherwise stated. ED: emergency department; MAP: mean arterial pressure; S_{cv,O_2}: central venous oxygen saturation; S_{v,O_2}: mixed venous oxygen saturation; ICU: intensive care unit. [#]: n=3,332; [¶]: n=2,807; [+]: Pearson's Chi-squared test.

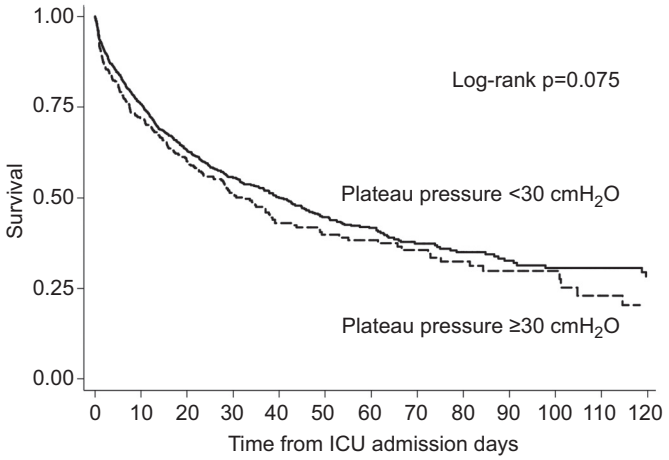

FIGURE 2. Kaplan–Meier hospital survival analysis for acute lung injury septic patients with or without a protective strategy in mechanical ventilation (censored to 120 days). ICU: intensive care unit.

format for use at most institutions to create customised protocols and pathways specific to their institutions. The implementation of SCC guideline recommendations, as evidenced by improvement in compliance with bundle targets, in patients with severe sepsis/septic shock has been shown to be associated with improved outcomes [7]. The implementation of the severe sepsis performance improvement programme has been extensively reported and targeted to assure aggressive haemodynamic resuscitation in other settings and countries [11, 12]. MURPHY *et al.* [13] reported from 212 patients with ALI complicating septic shock that early and late conservative late fluid management was associated with better patient outcomes, and SAKR *et al.* [14] reported from 3,147 patients included in the SOAP (Sepsis Occurrence in Acutely Ill Patients) study that high tidal volumes and positive fluid balance were associated with a worse outcome from ALI/acute respiratory distress syndrome (ARDS). However, outcome data on protective lung strategies based on limiting inspiratory plateau pressures in severe sepsis/septic shock patients are still lacking.

Lung-protective ventilation, a strategy that targets lower tidal volumes and limits plateau pressure to <30 cmH_2O, may be applied with either volume- or pressure-controlled ventilation in order to avoid acute parenchymal lung injury and a release of cytokines into alveoli and the systemic circulation [15] that may contribute to multiple organ dysfunction. Lung-protective ventilation strategies attempt to avoid these consequences by limiting peak lung distension and preventing end-expiratory collapse [16]. An important question might be to determine whether the severity of the respiratory failure is related to a lower compliance that results in higher plateau pressures. In some clinical settings, it is not clear whether a higher mortality might be due to a higher plateau pressure or a higher severity, or based on the different clinical management provided. In the present study, as a parameter for disease severity on admission, no differences were found in patients with or without a plateau pressure <30 cmH_2O were observed in the number of organ dysfunction. In addition, lung-protective ventilation strategies have been recommended in order to prevent tidal alveolar collapse and over-distension in patients with ALI/ARDS, and are the only clinical interventions to demonstrate a mortality benefit in published studies [4, 17, 18]. In addition, lung-protective strategy represents a physiologically sound and proven ventilation mode in order to avoid ventilator-induced lung injury (VILI) [19]. VILI injury caused by mechanical ventilation can lead to volutrauma, barotrauma and atelectrauma [20]. All of these mechanisms may initiate biophysical and biochemical injuries that increase alveolar–capillary permeability and a release of inflammatory mediators, and has been implicated in the concept of ''biotrauma'' [21]. In patients with sepsis and ALI, the release of mediators into the systemic circulation with subsequent systemic inflammation may contribute to the multiple organ failure and subsequent death of some patients [22, 23]. Lung-protective ventilation strategies have been associated with a more rapid attenuation of the inflammatory response in patients with ALI [24]. Lung-protective ventilation strategies might, in part, attenuate this overwhelming systemic inflammatory response syndrome triggered by a highly virulent pathogen. In addition, between 37% and 40% of the patients received protective ventilation while in the ICU if their sepsis was discovered in the emergency department or the ward. If the patient's sepsis was discovered while in the ICU, only 22% received protective ventilation. We suspect the reason for this is based on the nature of the patient admitted to each setting. Patients from ICU suffered a significantly higher number of organ failure than patients from the ward and emergency department. Based on the data extracted from the results of the SCC study [7], the mortality of the patients that developed

TABLE 5 Random-effects Cox proportional hazard[#] regression of plateau pressure <30 cmH_2O in patients with acute lung injury

	Observations n	Mortality HR (95% CI)	p-value
Unadjusted	1737	0.88 (0.75–1.03)	0.111
Adjusted[¶]	1737	0.84 (0.72–0.99)	0.038

HR: hazard ratio. [#]: shared gamma frailty model; [¶]: for region, sepsis admission source (emergency department, ward or intensive care unit), drotrecogin alfa administered within 24 h, vasopressor use (no, yes or not applicable), number of organ failures and site quarter.

TABLE 6 Random-effects Cox proportional hazard[#] regression of plateau pressure <30 cmH_2O in patients without acute lung injury

	Observations n	Mortality HR (95% CI)	p-value
Unadjusted	6139	0.78 (0.71–0.86)	<0.001
Adjusted[¶]	6139	0.77 (0.70–0.85)	<0.001

HR: hazard ratio. [#]: shared gamma frailty model; [¶]: for region, sepsis admission source (emergency department, ward or intensive care unit), drotrecogin alfa administered within 24 h, vasopressor use (no, yes or not applicable), number of organ failures, pneumonia and site quarter.

sepsis in the emergency department was 27.6% compared with 41.3% in the ICU. The multivariable mortality prediction model also demonstrated that the ICU, compared with the emergency department as the admission source, was independently associated with a worse outcome (OR 1.37, 95% CI 1.27–1.48; $p<0.0001$).

An important point to consider based on our results is that patients mechanically ventilated patients without ALI had also a better outcome when a protective mechanical ventilation strategy based approach using a plateau pressure <30 cmH_2O was implemented. GAJIC *et al.* [25] found that from 332 patients who did not have acute lung injury from the outset that the main risk factors associated with the development of ALI were the use of a large tidal volume. Along the same line, DETERMANN *et al.* [26] performed a randomised controlled unblinded preventive trial comparing mechanical ventilation with conventional *versus* lower tidal volume in critically ill patients without ALI at the onset of mechanical ventilation. Baseline plasma interleukin (IL)-6 levels were comparable in both study groups (median 50 (interquartile range 21–122) *versus* 51 (interquartile range 20–182) $ng \cdot mL^{-1}$ in the conventional and lower tidal volume groups, respectively; $p=0.74$). In the conventional tidal volume group, plasma IL-6 levels decreased after 4 days (21 (9–99) $ng \cdot mL^{-1}$), but the decrease over time was more pronounced in the lower tidal volume group (11 (5–20) $ng \cdot mL^{-1}$) ($p=0.01$). Interestingly, the trial was stopped prematurely for safety reasons because the development of lung injury was higher in the conventional tidal volume group as compared with the lower tidal volume group (13.5% *versus* 2.6%, $p=0.01$).

This study has several strengths. First, the analysis was conducted in a large number of patients. In addition, the cohort comprised a homogenous population with severe sepsis. Secondly, the patients included in the analysis represented a population that fairly represents a systematic but realistic approach that differs from randomised clinical trials with a probable selection bias [24, 26, 27]. Thirdly, the present study has assessed not only the impact of an inspiratory pressure-limited approach to mechanical ventilation in septic patients alone but also the beneficial effect of management with the compliance with applicable elements of sepsis management bundles.

The present study has several potential limitations that should be addressed. The first is inherent in its observational design. Patients included in the present study were based on a voluntary, self-selected (by institution) basis and not randomised; therefore, the possibility of unforeseen and unmeasured biases that could affect the results are possible. Secondly, some of the patients might be not accurately included in the ALI group since only a clinical assessment was used to determine the presence of noncardiac pulmonary oedema and other characteristics, such as the number of lung quadrants involved on chest radiography, were not recorded. Strengthening this clinical assessment was the exclusion of cardiac postoperative, COPD and pre-existing lung disease patients in order to improve accuracy of diagnosis. Thirdly, several confounding factors, potentially justifying the use of higher tidal volume, were not recorded (and thus not taken into account). Severe acidosis or associated brain injury may require higher tidal volume; increased abdominal pressure may lead to increased plateau pressure for a given tidal volume. Improved understanding of the mechanisms underlying VILI and barotrauma makes it imperative to control higher tidal volume in order to prevent alveolar overdistension. There still exits a reasonable controversy regarding the optimal tidal volume for ventilation and the best parameter to monitor its effect (*i.e.* plateau pressure). Current practice involves tidal volumes that are lower than those used in the past. The use of low tidal volume and limiting plateau pressure might represent ''two faces of the same coin''. Fourthly, because the level of positive end-expiratory pressure (PEEP) was not recorded, the distension pressure was unknown. However, a recent meta-analysis [28] of trials comparing higher *versus* lower levels of PEEP in adults with ARDS revealed that a significant statistical difference in hospital mortality was not observed between groups. However, higher levels were associated with improved survival among the subgroup of patients with ARDS, the answer in patients with ALI is still unknown. Finally, in the present study and based on the epidemiological approach, several factors influencing mechanical ventilation setting and outcome have not been considered (the period of time during which the plateau pressure was >30 cmH_2O, modalities of mechanical ventilation, the use of neuromuscular blockade, protocols of sedation, *etc.*).

In summary, the present study shows that the development of ALI in sepsis was associated with higher mortality. A protective mechanical ventilation strategy based approach has previously demonstrated a better outcome in heterogeneous populations of patients affected by ALI/ARDS. The implementation of inspiratory pressure-limited mechanical ventilation approach strategies in patients with severe sepsis with or without ALI was associated with improved survival. Our data suggest that this strategy should be strongly incorporated in performance metrics for management of septic patients with or without ALI.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1334–1349.
2 Hudson LD, Milberg JA, Anardi D, *et al.* Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995; 151: 293–301.
3 Rubenfeld GD, Caldwell E, Peabody E, *et al.* Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; 353: 1685–1693.
4 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1301–1308.
5 Sheu C-C, Gong MN, Zhai R. Clinical characteristics and outcomes of sepsis-related *vs* non-sepsis-related ARDS. *Chest* 2010; 138: 559–567.
6 Hudson LD. Epidemiology of the adult respiratory distress syndrome. *Semin Respir Crit Care Med* 1994; 15: 254–259.
7 Levy MM, Dellinger RP, Townsend SR, *et al.* The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 2010; 36: 222–231.

8 Levy MM, Fink MP, Marshall JC, *et al.* 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.
9 Dellinger RP, Carlet JM, Masur H, *et al.* Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Intensive Care Med* 2004; 30: 536–555.
10 Dellinger RP, Levy MM, Carlet JM, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008; 34: 17–60.
11 Ferrer R, Artigas A, Levy MM, *et al.* Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA 2008 21*, 299: 2294–2303.
12 Rivers EP. Point: adherence to early goal-directed therapy: does it really matter? Yes. After a decade, the scientific proof speaks for itself. *Chest* 2010; 138: 476–480.
13 Murphy CV, Schramm GE, Doherty JA, *et al.* The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009; 136: 102–109.
14 Sakr Y, Vincent JL, Reinhart K, *et al.* High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest* 2005; 128: 3098–3108.
15 Ranieri VM, Suter PM, Tortorella C, *et al.* Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. *JAMA* 1999; 282: 54–61.
16 Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2007; 18: CD003844.
17 Amato MB, Barbas CS, Medeiros DM, *et al.* Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338: 347–354.
18 Phua J, Badia JR, Adhikari NK, *et al.* Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med* 2009; 179: 220–227.
19 Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998; 157: 294–323.
20 Slutsky AS. Lung injury caused by mechanical ventilation. *Chest* 1999; 116: Suppl. 1, 9S–15S.
21 Chu EK, Whitehead T, Slutsky AS. Effects of cyclic opening and closing at low- and high-volume ventilation on bronchoalveolar lavage cytokines. *Crit Care Med* 2004; 32: 168–174.
22 Zhang H, Downey GP, Suter PM, *et al.* Conventional mechanical ventilation is associated with bronchoalveolar lavage-induced activation of polymorphonuclear leukocytes: a possible mechanism to explain the systemic consequences of ventilator-induced lung injury in patients with ARDS. *Anesthesiology* 2002; 97: 1426–1433.
23 Murphy DB, Cregg N, Tremblay L, *et al.* Adverse ventilatory strategy causes pulmonary-to-systemic translocation of endotoxin. *Am J Respir Crit Care Med* 2000; 162: 27–33.
24 Parsons PE, Eisner MD, Thompson BT, *et al.* Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med* 2005; 33: 1–6.
25 Gajic O, Dara SI, Mendez JL, *et al.* Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; 32: 1817–1824.
26 Determann RM, Royakkers A, Wolthuis EK, *et al.* Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Crit Care* 2010; 14: R1.
27 Sevransky JE, Levy MM, Marini JJ. Mechanical ventilation in sepsis-induced acute lung injury/acute respiratory distress syndrome: an evidence-based review. *Crit Care Med* 2004; 32: Suppl, S548–S553.
28 Briel M, Meade M, Mercat A, *et al.* Higher *vs* lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010; 303: 865–873.