


SEVEN-DAY PROFILE PUBLICATION



Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study

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Abstract

Purpose: To improve the outcome of the acute respiratory distress syndrome (ARDS), one needs to identify potentially modifiable factors associated with mortality.

Methods: The large observational study to understand the global impact of severe acute respiratory failure (LUNG SAFE) was an international, multicenter, prospective cohort study of patients with severe respiratory failure, conducted in the winter of 2014 in a convenience sample of 459 ICUs from 50 countries across five continents. A pre-specified secondary aim was to examine the factors associated with outcome. Analyses were restricted to patients (93.1 %) fulfilling ARDS criteria on day 1–2 who received invasive mechanical ventilation.

Results: 2377 patients were included in the analysis. Potentially modifiable factors associated with increased hospital mortality in multivariable analyses include lower PEEP, higher peak inspiratory, plateau, and driving pressures, and increased respiratory rate. The impact of tidal volume on outcome was unclear. Having fewer ICU beds was also associated with higher hospital mortality. Non-modifiable factors associated with worsened outcome from ARDS included older age, active neoplasm, hematologic neoplasm, and chronic liver failure. Severity of illness indices including lower pH, lower PaO₂/FiO₂ ratio, and higher non-pulmonary SOFA score were associated with poorer outcome. Of the 578 (24.3 %) patients with a limitation of life-sustaining therapies or measures decision, 498 (86.0 %) died in hospital. Factors associated with increased likelihood of limitation of life-sustaining therapies or measures decision included older age, immunosuppression, neoplasia, lower pH and increased non-pulmonary SOFA scores.

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The LUNG SAFE investigators and National coordinators are listed in Appendix 1 and 2 of the supplementary materials.

Take-home message: In patients enrolled in LUNG SAFE, potentially modifiable factors associated with survival include higher PEEP, lower peak inspiratory, plateau, and driving pressures, and lower respiratory rate. Non-modifiable factors associated with worse outcome from ARDS included older patient age, active neoplasm, hematologic neoplasm, and chronic liver failure.

Conclusions: Higher PEEP, lower peak, plateau, and driving pressures, and lower respiratory rate are associated with improved survival from ARDS.

Trial Registration: ClinicalTrials.gov NCT02010073.

Keywords: Acute respiratory distress syndrome, Positive end-expiratory pressure, Patient outcome, Driving pressure, Peak inspiratory pressure

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by acute inflammatory lung injury, associated with increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue [1].

The large observational study to understand the global impact of severe acute respiratory failure (LUNG SAFE) was recently undertaken in 459 intensive care units (ICUs) in 50 countries in five continents [2]. The results showed that ARDS continues to represent a global public health problem, occurring in 10 % of patients admitted to ICUs. ARDS was under-recognized by clinicians, while the use of contemporary evidence-based ventilatory strategies and adjuncts was lower than expected. Of most concern, ARDS continues to confer a high mortality, with 40 % of patients with ARDS dying in hospital. The wide geographic spread of participating ICUs, the large patient sample size, and the use of the Berlin criteria to classify patients independent of clinician recognition are important strengths of this study [2].

A key pre-specified secondary aim of the LUNG SAFE study was to examine the factors associated with outcomes in patients with ARDS in the era of the Berlin definition of ARDS. We were particularly interested in identifying potentially modifiable risk factors, such as those relating to patient management. In particular, we wished to understand the relationship between ventilator-related parameters and patient outcome from ARDS. In addition, we wished to determine the contribution of demographic factors, ARDS risk factors, and illness severity to patient outcome, as well as the factors associated with decisions to limit care.

Methods and materials

Study design

The detailed methods and protocol have been published elsewhere [2]. In brief, LUNG SAFE was an international, multicenter, prospective cohort study, with a 4-week enrollment window in the winter season [2]. The study, funded by the European Society of Intensive Care Medicine (ESICM), was endorsed by multiple national societies/networks (Appendix 1). All participating ICUs obtained ethics committee approval, and either patient consent or ethics committee waiver of consent. National coordinators (Appendix 1) and site investigators (Appendix 2) were

responsible for obtaining ethics committee approval and for ensuring data integrity and validity.

Patients, study design, and data collection

Inclusion criteria were admission to a study ICU (including ICU transfers) within the 4-week enrollment window and receipt of invasive or noninvasive ventilation (NIV). Exclusion criteria were age less than 16 years or inability to obtain informed consent, where required. Patients were classified as having ARDS on the basis of whether or not they fulfilled all of the Berlin criteria rather than by clinician determination, as previously described [2]. To ensure a more homogenous dataset, we restricted subsequent analyses to the large subset of patients (93.1 %) that fulfilled ARDS criteria on day 1 or day 2 following the onset of acute hypoxemic respiratory failure (AHRF) and who received invasive mechanical ventilation (Fig. 1). All data were recorded for each patient at the same time each day within participating ICUs, normally as close as possible to 10 a.m. each day. Data on ventilatory settings were recorded simultaneously with arterial blood gas analysis.

Data definitions

We defined ARDS severity according to the Berlin definition: mild ($\text{PaO}_2/\text{FiO}_2$ ratio 201–300 mmHg), moderate ($\text{PaO}_2/\text{FiO}_2$ ratio 101–200 mmHg), and severe ($\text{PaO}_2/\text{FiO}_2$ ratio ≤ 100 mmHg). ICU and hospital survival were evaluated at ICU or hospital discharge, or at day 90, whichever occurred first.

Patients were considered to have a pulmonary etiology of their ARDS if they had one or more pulmonary risk factors (e.g., pneumonia, aspiration, lung contusion, inhalation injury), and to have an extrapulmonary etiology if they had one or more non-pulmonary risk factors (e.g., systemic sepsis, burn, blood transfusion). Patients with both types of risk factors were considered as a separate category.

Driving pressure was defined as plateau pressure minus PEEP, and was calculated only in patients who had no evidence for spontaneous ventilation, i.e., where set and measured respiratory rates were equal ($N = 742$ patients).

Data management and statistical analyses

Descriptive statistics included proportions for categorical and mean (standard deviation) or median (interquartile range) for continuous variables. The amount of missing

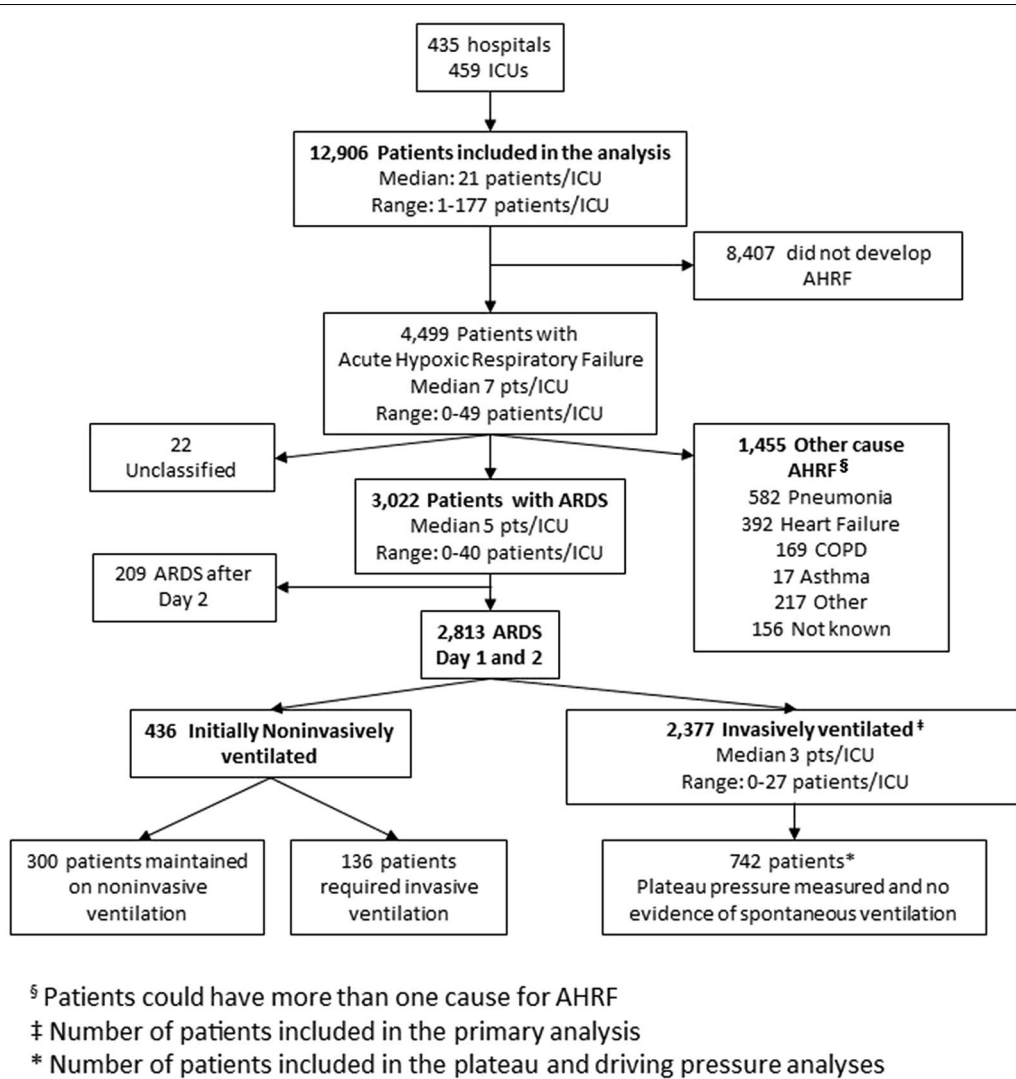


Fig. 1 Flowchart of patient's screening and enrollment. Data on 12,906 ventilated patients enrolled during the study period were analyzed. 4,499 patients developed acute hypoxemic respiratory failure (AHRF), of which 3,022 fulfilled acute respiratory distress syndrome (ARDS) criteria according to the Berlin definition. In 22 "unclassified" patients it was not possible to determine whether they fulfilled the criteria for ARDS because of incomplete data. This report focuses on the 2,377 patients that developed ARDS within 1–2 days of developing AHRF and who were managed with invasive mechanical ventilation. For the analyses relating to driving and plateau pressure, we restricted the population to the patients in whom plateau pressure was measured and in whom there was no evidence of spontaneous ventilation ($N = 742$ patients)

data was low as previously reported [2], and no assumptions were made for missing data. Proportions were compared using Chi-squared or Fisher exact tests, and continuous variables were compared using *T*-test or Wilcoxon rank sum test, as appropriate. Shapiro–Wilks test was used to assess normality in data distribution.

In each ARDS severity category (mild, moderate, severe), we estimated the relative risk (RR) of ICU and hospital mortality stratifying the study sample according tidal volume (<8 ml/kg, ≥ 8 ml/kg), PEEP (<12 cmH₂O, ≥ 12 cmH₂O), driving pressure (<14 cmH₂O, ≥ 14 cmH₂O),

and plateau pressure (<25 cmH₂O, ≥ 25 cmH₂O) measured at ARDS onset. These thresholds were each defined a priori on the basis of previous studies [3–5] or, in the case of PEEP, a consensus decision.

To identify predictors of hospital and ICU mortality and limitation of life-sustaining therapies or measures decision during hospital stay, we conducted a bivariable analysis for each demographic factor, ARDS risk factor, patients' comorbidity, illness severity, and management factor measured on the day of ARDS onset and ICU organizational factors. A stepwise regression approach

with significance alpha levels of 0.05 (both for entry and retention) was used to establish a set of independent variables associated with mortality. Stepwise regression is an iterative process whereby we checked the statistical significance of all variables at each stage and the process ends when none of the effects outside the model has an *F* statistic significant at the entry probability level and every effect in the model is significant at the retention probability level. Results are shown as odds ratios (ORs) with 95 % confidence interval (CI).

A robust locally weighted scatter plot smoothing (LOWESS) method was applied to investigate the relationship between the proportion of deaths (in ICU and in hospital) and plateau pressure, driving pressure, peak inspiratory pressure, and PaO₂/FiO₂ ratio on the first day of ARDS. The smoothing curves used a bandwidth of 0.66, a polynomial regression with 1 degree of freedom, and a tricubic weight function so that observations furthest from the point of interest were assigned the least weight.

All *P*-values were two-sided, with *P*-values less than 0.05 considered as statistically significant. The study protocol and case report form are included in Appendix 3. Statistical analyses were performed with R, version 3.0.2 (R Project for Statistical Computing, <http://www.R-project.org>) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

As previously reported [2], 459 participating ICUs from 50 countries enrolled 4499 patients with AHRF to the LUNG SAFE study. This analysis is confined to the 2377 patients invasively ventilated and with ARDS diagnosed on day 1 (*n* = 2243) or day 2 (*n* = 134) following development of AHRF (Fig. 1). In-hospital mortality was 35 % in patients with mild ARDS, 40 % in moderate ARDS, and 46 % in severe ARDS.

Factors contributing to outcome from ARDS

Table 1 reports the comparison of ARDS survivors (59.6 %) to non-survivors (40.4 %) at hospital discharge. The range of tidal volumes used was relatively narrow (Fig. e1) and the mean tidal volume used did not differ between survivors and non-survivors (Table 1). The unadjusted impact of ventilation-related variables in each severity category of ARDS is shown in Fig. 2. Hospital mortality risk was similar in patients with lower tidal volume [<8 cmH₂O ml/kg predicted body weight (PBW)] compared to those with higher tidal volume (Fig. 2a). In patients with moderate ARDS, patients with a lower PEEP (<12 cmH₂O) had a risk of hospital mortality 26 % greater than those observed in patients with higher PEEP [RR 1.26 (95 % CI 1.00–1.58)] (Fig. 2b). This

was not seen in mild or severe ARDS. Lower driving pressure (<14 cmH₂O) was associated with a decreased risk of hospital mortality in patients with moderate [RR 0.75 (95 % CI 0.59–0.96)] and severe [RR 0.67 (95 % CI 0.47–0.95)] ARDS, respectively (Fig. 2c). Lower plateau pressure (<25 cmH₂O) was associated with a decreased risk of hospital mortality in patients with severe ARDS [RR 0.69 (95 % CI 0.49–0.97)] (Fig. 2d). The relationships between tidal volume, PEEP, driving and plateau pressures and ICU mortality are shown in Fig. e2.

The factors included in the bivariable analyses for hospital mortality are listed in Table e1. In subsequent multivariate analyses, older age, active neoplasm, hematologic neoplasm, immunosuppression, and chronic liver failure were associated with increased hospital mortality (Table 2). Outcome was independent of pulmonary versus extrapulmonary etiology of ARDS (Table e1). Illness severity factors associated with worse outcome comprised lower pH, lower PaO₂/FiO₂ ratio, and higher non-pulmonary sequential organ failure assessment (SOFA) score (Table 2). Ventilation parameters including lower respiratory rate, higher PEEP, and lower peak inspiratory pressure were each associated with decreased hospital mortality. Tidal volume was not associated with outcome. A greater number of ICU beds was associated with improved hospital survival, but not ICU survival (Table e2). Similar findings were seen in analyses of factors associated with 28-day and with ICU survival (Tables e2 and e3). In multivariate analyses confined to patients who had “true” plateau pressure measured, i.e., those in whom there was no evidence for spontaneous ventilation (*N* = 742 patients), both higher driving pressure and higher plateau pressure were independently associated with worse hospital survival (Tables e4 and e5).

Patients with a driving pressure of equal to or greater than the median value 14 cmH₂O on day 1 of ARDS criteria had a higher mortality (*P* = 0.0124, log-rank test) (Fig. e3a). Patients with a plateau pressure equal to or greater than the median value of 23 cmH₂O on day 1 of ARDS criteria had a higher mortality (*P* = 0.0024, log-rank test) (Fig. e3b). There was no difference in survival in patients with a tidal volume of equal to or greater than the median value of 7.1 ml/kg/PBW (Fig. e3c).

Relationship between ventilator variables and outcome

Figure 3 shows the relationship between ventilation parameters on the first day of ARDS and the proportion of in-hospital deaths using LOWESS plots. The slope of the curves for risk of mortality increase at plateau pressures above 20 cmH₂O and again above 30 cmH₂O (Figs. 3a and e4a). For plateau pressures below 20 cmH₂O, there was no clear relationship with

Table 1 Comparison of survivors versus non-survivors at hospital discharge in invasively ventilated patients with ARDS (n = 2377)

	Alive (n = 1416)	Dead (n = 953)	All patients (n = 2377)*	P-value
Age (years)				
Mean (SD)	58.2 (16.8)	64.0 (16.4)	60.5 (16.9)	<0.001
Median (IQR)	60.0 (47.0–71.0)	67.0 (55.0–76.0)	63.0 (50.0–73.0)	
Male, n (%)	877 (61.9)	591 (62.0)	1472 (61.9)	0.969
ARDS risk factors, n (%)				
No risk factors	124 (8.76)	66 (6.93)	190 (7.99)	0.108
Only non-pulmonary	288 (20.3)	191 (20.0)	480 (20.2)	0.860
Only pulmonary	803 (56.7)	533 (55.9)	1342 (56.5)	0.707
Both	201 (14.2)	163 (17.1)	365 (15.4)	0.054
Patients with at least one pulmonary ARDS risk factors, n (%)	1004 (70.9)	696 (73.0)	1707 (71.8)	0.259
Risk factor for ARDS, n (%)				
Pneumonia	799 (56.4)	571 (59.9)	1375 (57.9)	0.092
Extrapulmonary sepsis	216 (15.3)	194 (20.4)	412 (17.3)	0.001
Aspiration	213 (15.0)	154 (16.2)	370 (15.6)	0.461
Trauma	85 (6.00)	22 (2.31)	107 (4.50)	<0.001
Inhalation	42 (2.97)	26 (2.73)	68 (2.86)	0.734
Pancreatitis	22 (1.55)	27 (2.83)	49 (2.06)	0.032
Pulmonary contusion	59 (4.17)	21 (2.20)	80 (3.37)	0.010
Burn	5 (0.35)	3 (0.31)	8 (0.34)	1.000
Pulmonary vasculitis	12 (0.85)	19 (1.99)	32 (1.35)	0.016
Non-cardiogenic shock	97 (6.85)	102 (10.7)	199 (8.37)	0.001
Drowning	1 (0.07)	1 (0.10)	2 (0.08)	1.000
Drug overdose	39 (2.75)	10 (1.05)	49 (2.06)	0.004
Blood transfusion	49 (3.46)	54 (5.67)	103 (4.33)	0.010
Other risk factors	49 (3.46)	20 (2.10)	69 (2.90)	0.053
Chronic disease, n (%)				
COPD	274 (19.4)	194 (20.4)	472 (19.9)	0.546
Chronic cardiac failure	119 (8.40)	103 (10.8)	224 (9.4)	0.049
Diabetes mellitus	292 (20.6)	220 (23.1)	515 (21.7)	0.153
Active neoplasm	89 (6.29)	107 (11.2)	199 (8.4)	<0.001
Hematologic neoplasm	26 (1.84)	80 (8.39)	107 (4.50)	<0.001
Chronic renal failure	113 (8.98)	110 (11.5)	224 (9.42)	0.004
Chronic liver failure	30 (2.12)	73 (7.66)	103 (4.33)	<0.001
Immuno-incompetence	136 (9.60)	150 (15.7)	294 (12.4)	<0.001
ARDS severity, n (%)				
Mild	461 (64.2)	250 (35.2)	714 (100)	0.001
Moderate	658 (59.6)	446 (40.4)	1106 (100)	0.874
Severe	297 (53.6)	257 (46.4)	557 (100)	0.001
Illness severity factors, mean (SD)				
pH	7.34 (0.10)	7.30 (0.14)	7.33 (0.12)	<0.001
PaCO ₂ (mmHg)	45.94 (14.18)	46.00 (16.03)	45.97 (14.97)	0.4866
FiO ₂	0.63 (0.23)	0.67 (0.24)	0.64 (0.23)	<0.001
SpO ₂ (%)	95.2 (4.47)	93.9 (6.54)	94.7 (5.46)	<0.001
PaO ₂ (mmHg)	94.1 (38.4)	92.1 (37.4)	93.3 (38.0)	0.079
PaO ₂ /FiO ₂ ratio (mmHg)	165 (68.2)	154 (67.2)	161 (68.0)	<0.001
SOFA score	9.02 (3.43)	11.08 (3.82)	9.87 (3.73)	<0.001
Non-pulmonary SOFA score	6.13 (3.35)	8.09 (3.75)	6.94 (3.65)	<0.001
SOFA score adjusted	9.25 (3.71)	11.3 (4.10)	10.1 (4.00)	<0.001

Table 1 continued

	Alive (n = 1416)	Dead (n = 953)	All patients (n = 2377)*	P-value
Non-pulmonary SOFA score adjusted	6.06 (3.62)	8.09 (4.11)	6.87 (3.95)	<0.001
SOFA score—central nervous system	1.98 (1.63)	2.31 (1.69)	2.12 (1.66)	<0.001
SOFA score—cardiovascular	1.95 (1.71)	2.63 (1.68)	2.23 (1.73)	<0.001
SOFA score—respiration	2.88 (0.72)	3.01 (0.73)	2.93 (0.73)	<0.001
SOFA score—coagulation	0.90 (1.28)	1.23 (1.40)	1.04 (1.34)	<0.001
SOFA score—liver	0.51 (0.91)	0.75 (1.12)	0.60 (1.01)	<0.001
SOFA score—renal	0.67 (1.08)	1.05 (1.19)	0.82 (1.14)	<0.001
Management factors, mean (SD)				
RR total (breaths/min)	20.3 (6.43)	21.6 (11.1)	20.8 (8.64)	<0.001
PEEP (cm H ₂ O)	8.49 (3.34)	8.36 (3.34)	8.44 (3.34)	0.243
Peak inspiratory pressure (cmH ₂ O)	26.5 (8.10)	27.9 (8.22)	27.0 (8.18)	<0.001
Tidal volume/PBW (mL/kg)	7.65 (1.87)	7.56 (1.90)	7.61 (1.88)	0.366
Minute ventilation (L/min)	9.39 (3.00)	9.64 (3.18)	9.49 (3.07)	0.104

Inclusion criteria: ARDS onset within 48 h from AHRF; patients received invasive mechanical ventilation in the first 48 h from ARDS onset

All clinical parameters were measured at ARDS onset

ARDS acute respiratory distress syndrome, COPD chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, RR respiratory rate, PEEP positive end-expiratory pressure, PBW predicted body weight, SD standard deviation, IQR interquartile range

* Vital status was evaluated at hospital discharge or at 90 days after onset of AHRF, which ever event occurred first. This information was missing for 8 patients (0.3 %)

hospital or ICU mortality. Mortality was relatively flat up to a driving pressure of 10 cmH₂O; above this value, mortality increased relatively linearly with increasing driving pressure (Figs. 3b and e4b). In contrast, while the slope of the curve of peak inspiratory pressure versus mortality increased at values over 40 cmH₂O, the curve did not flatten out below this value (Figs. 3c and e4c). For PaO₂/FiO₂ ratio, the relationship with mortality risk was relatively flat at ratios above 150 mmHg, but mortality risk increased at lower PaO₂/FiO₂ ratios (Figs. 3d and e4d).

Limitation of life-sustaining therapies or measures

Of the 578 (24.3 %) patients with a limitation of life-sustaining therapies or measures decision, 7 patients (1.2 %) had this decision in place prior to developing ARDS, while in 525 (90.8 %) patients, this decision was made at or after the development of ARDS. In 46 (8.0 %) patients, the timing of the decision was unclear (Fig. e5). Six of the seven patients with prior limitation of life-sustaining therapies or measures decision survived to hospital discharge. Overall, 498 (86 %) of patient with orders limiting care died in hospital.

In a bivariate analysis, increased age, immunosuppression, the presence of active or hematologic neoplasm, and chronic liver failure were each associated with increased likelihood of limitation of life-sustaining therapies or measures (Table 3). Disease severity factors including lower pH and higher adjusted non-pulmonary SOFA score were also associated with limitation of life-sustaining therapies or measures.

Discussion

The LUNG SAFE study is the largest epidemiologic study of patients with ARDS and acute hypoxic respiratory failure to date, with data on patients admitted to 459 ICUs in 50 countries across five continents. We found that older patient age, presence of neoplastic disease, and severity of illness markers such as lower pH, lower PaO₂/FiO₂ ratio, and higher non-pulmonary SOFA scores were associated with worsened patient outcome. Potentially modifiable factors associated with increased hospital mortality in multivariable analyses include lower PEEP, higher peak inspiratory, plateau, and driving pressures, increased respiratory rate, and lower number of ICU beds.

Factors contributing to outcome from ARDS

Our finding that older age was independently associated with worse outcome is in accord with multiple prior studies [6–8], and with prognosis scores such as the simplified acute physiology score (SAPS). The presence of risk factors such as active neoplasm, hematologic neoplasm, and chronic liver failure independently worsened outcome, and are largely consistent with prior studies [8, 9]. Severity of illness factors associated with worse outcome included lower pH, lower PaO₂/FiO₂ ratio, and increasing non-pulmonary SOFA score [8]. The lack of association between risk factor type, i.e., pulmonary versus extrapulmonary, and outcome from ARDS contrasts with some previous smaller studies [10], but is consistent with a prior meta-analysis [11].

We found that key aspects of ventilator management were associated with patient outcome. The use of higher PEEP in patients with moderate or severe ARDS was

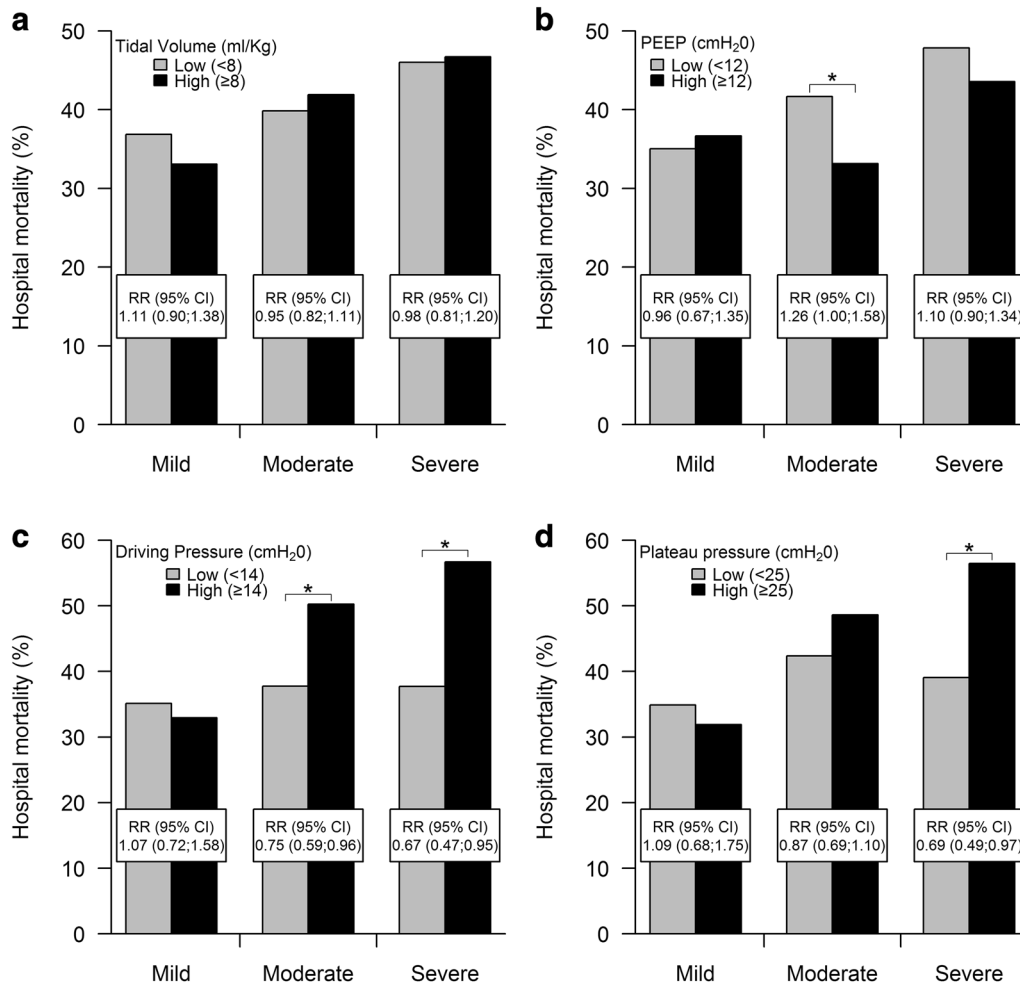


Fig. 2 Relationship between lower versus higher tidal volume, PEEP, driving pressure, and plateau pressure and hospital mortality. **a** There was no relationship between lower (<8 ml/kg PBW) versus higher (≥8 ml/kg PBW) tidal volume and hospital mortality in patients with mild, moderate, or severe ARDS. **b** In patients with moderate ARDS, lower PEEP (i.e., PEEP <12 cmH₂O) was associated with increased hospital mortality. This was not seen in mild or severe ARDS. **c** In patients with moderate and severe ARDS, higher driving pressure (i.e., ≥14 cmH₂O) was associated with increased hospital mortality. This was not seen in mild ARDS. **d** In patients with severe ARDS, higher plateau pressure (i.e., ≥25 cmH₂O) was associated with increased hospital mortality. This was not seen in mild or moderate ARDS. **P*-value < 0.05, comparison between risks. Mortality is defined as mortality at hospital discharge or at 90 days after onset of AHRF, whichever event occurred first. All clinical independent parameters were measured at ARDS onset. Driving pressure analysis confined to patients in whom plateau pressure was measured and in whom there was no evidence of spontaneous ventilation (*N* = 742 patients). All other analyses completed on the entire patient dataset (*n* = 2377 patients). *RR* relative risk, *CI* confidence interval

independently associated with improved hospital survival, supporting prior findings from an individual patient data meta-analysis [12], as well as a preponderance of preclinical evidence suggesting benefits with higher PEEP particularly in more severe ARDS.

The lack of a relationship between tidal volume and outcome in our patients likely reflects the relatively limited range of tidal volumes used, which was concentrated in a range around a median of 7.1 ml/kg. In particular, the use of tidal volumes below 6 or above 10 ml/kg PBW was relatively low in these patients. In addition, there may be

a potential confounding effect of the use of lower tidal volumes in more severely ill patients, which is difficult to fully dissect out in an observational dataset such as this. Our data does not imply that tidal volume is unimportant, but rather suggests the widespread adoption of lower tidal volume ventilation. We know from large well-conducted prospective randomized clinical trials that reducing tidal volume is a key component of protective lung ventilation and saves lives [3, 13].

The association between peak, plateau, and driving pressures and both hospital and ICU outcome also

Table 2 Factors associated with hospital mortality in invasively ventilated patients (n = 2377)

Parameter	Multivariate model (n = 2091)	
	OR (95 % CI)	p-value
Demographic factors		
Age	1.03 (1.019–1.032)	<0.001
Risk factors		
Active neoplasm		
Yes (ref. no)	1.83 (1.31–2.57)	<0.001
Immunosuppression		
Yes (ref. no)	1.42 (1.04–1.93)	0.027
Hematologic neoplasm		
Yes (ref. no)	4.77 (2.82–8.04)	<0.001
Chronic liver failure		
Yes (ref. no)	3.28 (1.99–5.40)	<0.001
Illness severity factors		
pH	0.12 (0.05–0.29)	<0.001
PaO ₂ /FiO ₂ ratio (mmHg)	0.998 (0.997–1.000)	0.025
Non-pulmonary SOFA score adjusted	1.12 (1.09–1.15)	<0.001
Management factors		
RR total (breaths/min)	1.03 (1.01–1.04)	0.003
PEEP (cmH ₂ O)	0.95 (0.92–0.98)	0.001
Peak inspiratory pressure (cmH ₂ O)	1.02 (1.01–1.04)	0.002
ICU organizational factors		
Number of beds	0.99 (0.99–1.00)	0.035

The term ref. indicates the reference group useful to interpret the model parameter and the estimate of odds ratio

Hospital mortality is defined as mortality at hospital discharge or at 90 days after onset of AHRF, whichever event occurred first. This information was missing for 8 patients (0.3 %)

Inclusion criteria: ARDS onset within 48 h from AHRF; patients received invasive mechanical ventilation in the first 48 h from ARDS onset

All clinical independent parameters (pH, FiO₂, SOFA score, etc.) were measured at ARDS onset

PaCO₂ not included in stepwise selection process for this analysis. SpO₂, SOFA score, non-pulmonary SOFA score not included in stepwise selection because there were many missing values (35.6, 42.3, and 42.3 %, respectively)

ARDS acute respiratory distress syndrome, SOFA sequential organ failure assessment, RR respiratory rate, PEEP positive end-expiratory pressure, ICU intensive care unit, OR odds ratio, CI confidence interval

confirms prior findings [14]. The finding of a positive association between lower respiratory rate and patient outcome is a novel finding, and is supported by prior experimental data [15, 16]. This finding may support the hypothesis that energy transfer to the lung is an important contributor to ventilator-induced lung injury [17, 18].

Relationships between ventilatory parameters and outcome

The LOWESS curve of the relationship between plateau pressure and the risk of ICU and hospital death did appear to flatten out below 20 cmH₂O. This finding contrasts with that of Hager et al., who did not find a lower “safe” plateau pressure [19]. In relation to driving pressure, the proportion of deaths increased relatively linearly at pressures above 10 cmH₂O, while the curve is flat below this value. These findings are suggestive of

the potential utility of this index as a prognostic index in non-trial, “real world” patients [14]. It is important to note that we classified driving pressure and plateau pressures as potentially modifiable but they also contain an important element that depends on the patient’s lung injury severity. The inflection in the relationship between PaO₂/FiO₂ ratio and mortality observed at values around 120–150 mmHg supports the empirical decisions of selecting these values for enrollment in clinical trials [20] or secondary analyses [21].

The finding that lower ICU bed number was associated with higher hospital, but not ICU, mortality is of concern. It suggests that ICU organizational factors and/or resource constraints may impact on ICU discharge decisions, and hence on patient outcome. It supports older studies demonstrating that patients discharged from ICU at times of high bed occupancy are sicker and have had a shorter ICU stay than patients discharged when more

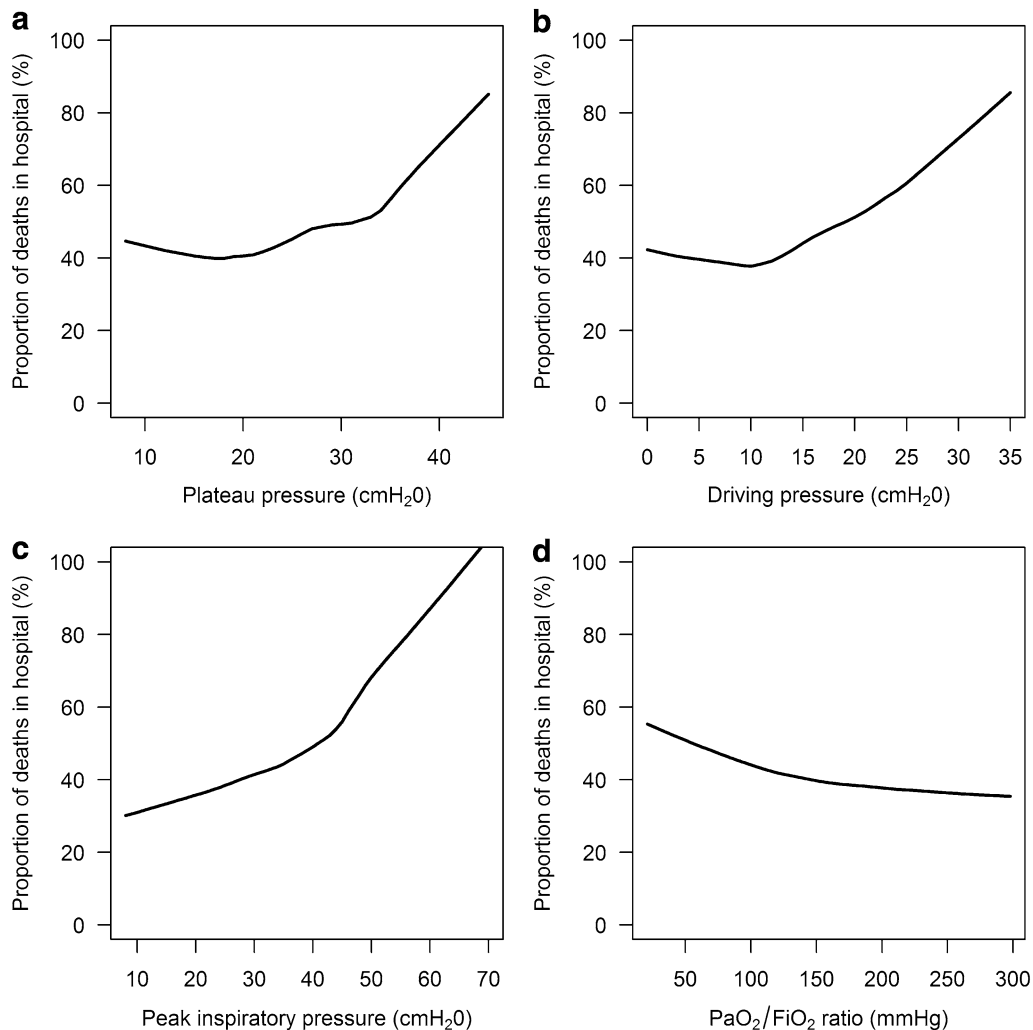


Fig. 3 Relationship between ventilation parameters and hospital mortality. Robust locally weighted regression and smoothing (LOWESS) plot (bandwidth 2/3, 1 degree of polynomial regression) of hospital mortality and plateau pressure (**a**), driving pressure (**b**), peak inspiratory pressure (**c**), and PaO₂/FiO₂ ratio (**d**) measured on the first day of ARDS onset. Mortality is defined as mortality at hospital discharge or at 90 days after onset of AHRF, whichever event occurred first. All clinical independent parameters were measured at ARDS onset. Plateau pressure and driving pressure analyses confined to patients in whom plateau pressure was measured and in whom there was no evidence of spontaneous ventilation ($N = 742$ patients). All other analyses completed on the entire patient dataset ($n = 2377$ patients)

beds were available [22]. Prior studies also demonstrate that a significant proportion of patients that die in hospital following ICU discharge were expected to live at the time of ICU discharge [23, 24].

Limitation of life-sustaining therapies or measures

The majority of decisions to limit care were made after development of ARDS. Interestingly, survival in the small proportion of patient that had a limitation of life-sustaining therapies or measures decision prior to developing ARDS was surprisingly high. Less surprising was the fact that 86 % of patients in whom decisions to limit care were

made after the development of ARDS died in hospital. Increased age and the presence of active or hematologic neoplasm, immune suppression, chronic liver failure, and indices of greater illness severity were associated with limitation of life-sustaining therapies or measures, consistent with prior findings [25]. Overall, there were similarities between the factors associated with patient outcome and those associated with limitation of life-sustaining therapies or measures. This may be consistent with the fact that death in the ICU not infrequently occurs in the context of decisions to limit life-sustaining therapies or measures as a result of perceived futility [26, 27].

Table 3 Bivariate logistic regression analysis of factors associated with limitation of life-sustaining therapies or measures in invasively ventilated patients (n = 2377)

Parameter	Bivariate models	
	OR (95 % CI)	p value
Demographic factors		
Age (years)	1.03 (1.02–1.03)	<0.001
Gender		
Male (ref. female)	0.95 (0.79–1.16)	0.626
Risk factors		
Pulmonary ARDS risk factors		
Yes (ref. no)	1.01 (0.82–1.25)	0.922
Pneumonia		
Yes (ref. no)	1.04 (0.87–1.25)	0.724
Non-pulmonary ARDS risk factors		
Yes (ref. no)	0.99 (0.78–1.25)	0.932
Non-pulmonary sepsis		
Yes (ref. no)	1.24 (0.97–1.57)	0.081
No ARDS risk factors		
Yes (ref. no)	0.99 (0.70–1.41)	0.972
ARDS risk factors		
Only pulmonary (ref. none)	1.00 (0.67–1.48)	0.991
Only non-pulmonary (ref. none)	1.01 (0.71–1.44)	0.963
Both (ref. none)	1.01 (0.67–1.52)	0.964
COPD		
Yes (ref. no)	1.05 (0.83–1.32)	0.697
Diabetes mellitus		
Yes (ref. no)	1.07 (0.85–1.34)	0.580
Chronic renal failure		
Yes (ref. no)	1.34 (0.99–1.81)	0.060
Active neoplasm		
Yes (ref. no)	1.70 (1.25–2.31)	0.001
Immunosuppression		
Yes (ref. no)	1.71 (1.31–2.23)	<0.001
Hematologic neoplasm		
Yes (ref. no)	2.37 (1.59–3.51)	<0.001
Chronic heart failure		
Yes (ref. no)	1.28 (0.94–1.73)	0.120
Chronic liver failure		
Yes (ref. no)	2.53 (1.70–3.79)	<0.001
Home ventilation		
Yes (ref. no)	0.97 (0.45–2.05)	0.928
Active or hematologic neoplasm or immunosuppression		
Yes (ref. no)	1.72 (1.38–2.13)	<0.001
COPD or home ventilation		
Yes (ref. no)	1.06 (0.84–1.33)	0.628
Illness severity factors		
pH	0.21 (0.10–0.45)	<0.001
FiO ₂	0.87 (0.59–1.31)	0.509
SpO ₂ (%)	0.99 (0.97–1.01)	0.213
PaO ₂ (mmHg)	0.998 (0.996–1.001)	0.222

Table 3 continued

Parameter	Bivariate models	
	OR (95 % CI)	p value
PaO ₂ /FiO ₂ ratio (mmHg)	1.000 (0.999–1.001)	0.934
SOFA score		
Non-pulmonary SOFA score	1.10 (1.06–1.13)	<0.001
SOFA score adjusted	1.08 (1.05–1.10)	<0.001
Non-pulmonary SOFA score adjusted	1.08 (1.05–1.11)	<0.001
SOFA score—central nervous system	1.08 (1.02–1.15)	0.011
SOFA score—cardiovascular	1.13 (1.07–1.20)	<0.001
SOFA score—respiration	1.01 (0.89–1.15)	0.886
SOFA score—coagulation	1.12 (1.05–1.20)	0.001
SOFA score—liver	1.20 (1.08–1.32)	<0.001
SOFA score—renal	1.19 (1.10–1.30)	<0.001
ICU organizational factors		
Number of beds	0.99 (0.99–1.00)	0.063
Beds per physician	1.01 (0.99–1.03)	0.397
Beds per nurse	1.01 (0.96–1.06)	0.677

The term ref. indicates the reference group useful to interpret the model parameter and the estimate of odds ratio

Inclusion criteria: ARDS onset within 48 h from AHRF; patients received invasive mechanical ventilation in the first 48 h from ARDS onset

All clinical independent parameters were measured at ARDS onset

ARDS acute respiratory distress syndrome, COPD chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, RR respiratory rate, PEEP positive end-expiratory pressure, ICU intensive care unit, OR odds ratio, CI confidence interval

Limitations

This study has a number of limitations. Our focus on winter months, while allowing us to examine the burden of ARDS during the same season across the globe, and our convenience sample approach may be prone to selection biases that may limit generalizability in regard to factors associated with ARDS outcome. Similar to other epidemiologic studies, we did not have access to the source data for the patients in the enrolling ICUs, and it is possible that some patients with hypoxemia, and thus ARDS, in participating centers were missed. It is important to stress, however, that ICUs were participating whether or not they identified any patient having ARDS and that the diagnosis of ARDS was not based on chart records. In addition, enrollment of patients with ARDS from participating ICUs met expectations based on their recorded 2013 admission rates, while data from lower recruiting ICUs were not different from higher enrolling ICUs, suggesting the absence of reporting biases. While we classified ventilator-related variables as potentially modifiable, it is important to acknowledge that non-modifiable factors, particularly disease severity, also play an important role in ventilator settings. In addition, we did not ask investigators how they measured total PEEP, and it is possible that total PEEP was not measured after

end-expiratory occlusion in some patients, which may have led to an overestimation of plateau and driving pressure in some patients. To ensure data quality, we instituted a robust data quality control program in which all centers were requested to verify data that appeared inconsistent or erroneous. The absence of data on other aspects of ICU management, e.g., fluid therapy, may limit the conclusions that can be drawn. Lastly, our assumptions that patients discharged from the hospital before day 28 were alive at that time point and that inpatients at day 90 survived to hospital discharge are further limitations.

Conclusions

In this prospective study carried out in ICUs across 50 countries, potentially modifiable factors associated with increased hospital mortality in multivariable analyses include lower PEEP, higher peak inspiratory, plateau and driving pressures, increased respiratory rate, and a lower number of ICU beds. These findings provide insight into current management practices in relation to ARDS and relationships between modifiable and non-modifiable factors and patient outcome from ARDS.

Electronic supplementary material

The online version of this article (doi:[10.1007/s00134-016-4571-5](https://doi.org/10.1007/s00134-016-4571-5)) contains supplementary material, which is available to authorized users.

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Acknowledgments

Funding/support: This work was funded and supported by the European Society of Intensive Care Medicine (ESICM), Brussels, Belgium, by St Michael's Hospital, Toronto, Canada, and by the University of Milan-Bicocca, Monza, Italy.

Role of the funders: The ESICM provided support in data collection and study coordination. ESICM, St Michael's Hospital, and University of Milan-Bicocca had no role in the design and conduct of the study; management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Compliance with ethical standards

Conflicts of interest

The authors attest that they have no conflicts of interest in regard to the subject of this manuscript.

Received: 6 July 2016 Accepted: 22 September 2016

Published online: 18 October 2016

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