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Early View

Original article

Demographics, management and outcome of women and men with Acute Respiratory Distress Syndrome in the LUNG SAFE prospective cohort study

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Running title: Sex differences management and outcomes in ARDS

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Take Home message: Shorter females with ARDS were less likely to receive lower tidal volume ventilation than shorter men, while mortality rates were significantly higher in women with confirmed severe ARDS. Better ventilatory management may improve outcomes in females with ARDS.

Plain Language Summary: Important sex differences exist in the management and outcomes of patients with Acute Respiratory Distress Syndrome (ARDS). Only half of females received lower tidal volumes, with shorter women more likely to receive higher tidal volumes compared to shorter men. Of particular concern, mortality rates were significantly higher in women with confirmed severe ARDS. These findings highlight the potential for better ventilatory management in females to improve their outcomes from ARDS.

Abstract

Rationale: We wished to determine the influence of sex on the management and outcomes in acute respiratory distress syndrome (ARDS) patients in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE).

Methods: We assessed the effect of sex on mortality, length of stay (LOS) and duration of invasive mechanical ventilation (IMV) in patients with ARDS who underwent IMV, adjusting for plausible clinical and geographic confounders.

Findings: Of 2,377 patients with ARDS, 905 (38%) were female while 1,472 (62%) were male. There were no sex differences in clinician recognition of ARDS, or critical illness severity profile. Females received higher tidal volumes (8.2 ± 2.1 vs. 7.2 ± 1.6ml/kg, $p<0.0001$), and higher plateau and driving pressures compared to males. Lower tidal volume ventilation was received by 50% of females compared to 74% of males $p<0.0001$). In shorter patients ($\leq$1.69 metres) females were significantly less likely to receive lower tidal volumes. Surviving females had a shorter duration of IMV and reduced LOS compared to males. Overall hospital mortality was similar in females (40.2%) versus males (40.2%). However, female sex was associated with higher mortality in patients with severe confirmed ARDS (odds ratio for sex (male versus female) 0.35, 95% confidence interval 0.14-0.83).

Interpretation: Shorter females with ARDS are less likely to receive lower tidal volume ventilation, while females with severe confirmed ARDS have a higher mortality risk. These data highlight the need for better ventilatory management in females to improve their outcomes from ARDS.

Introduction

Differences in the clinical management and outcomes of women versus men are well described [1]. The reasons underlying these differences are complex with biological, organizational, case-mix, ethnicity, socio-economic and local therapeutic traditions having an influence [2]. Differences related to age profile and disease severity and/or complexity may also play a role [3-5]. For example, females hospitalized with coronary artery disease are less likely to undergo invasive diagnostic and therapeutic intervention despite similar rates of presentation with acute myocardial infarction [1], but these differences may be related to older age at presentation. In females presenting with haemorrhagic stroke, the lower intervention rates is partially explained by more complex disease and older age at presentation [5].

In the critically ill, the impact of sex is less well understood. Sex may affect access to critical care, with women less likely to be admitted to intensive care unit (ICU) [6]. However, once in the ICU there have been few studies indicating sex bias in the provision of care [3, 6]. In a prospective study of ICU admissions in Austria, while women had greater illness severity, men were independently more likely to receive invasive procedures while outcomes were not different by sex [6]. Sex-based biological differences may influence development and/or management of acute respiratory distress syndrome (ARDS) [7-9]. Han and colleagues demonstrated that shorter patients (i.e. predominantly women) with severe sepsis-related acute lung injury received lung protective ventilation less frequently [10], a finding confirmed in an analysis of ARDS network trials [11]. Height is frequently inaccurately estimated, particularly in shorter patients [12], further increasing risk in females, given their shorter stature. Sex-specific hormonal differences can influence inflammation and immunological function [13, 14],

which may impact on risk of developing ARDS. The impact of sex on outcomes from ARDS is less clear [15-17].

We wished to address these issues in a secondary analysis of the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE), a global multicentre cohort study [7]. Our primary objective was to determine the impact of sex on outcomes from ARDS. Secondary objectives were to assess differences in clinician recognition, patient management and progression of ARDS by sex.

Methods

Study design, patients and data collection

The detailed methods and protocol for LUNG SAFE have been published elsewhere [7]. In brief, LUNG SAFE was an international, multicentre, prospective cohort study, conducted during with a four consecutive weeks in the winter of 2014 in a convenience sample of 459 ICUs from 50 countries across six continents [7]. The study, funded by the European Society of Intensive Care Medicine (ESICM), was endorsed by multiple national societies/networks (Appendix 1). National coordinators (Appendix 1) and site investigators (Appendix 1) were responsible for obtaining ethics committee approval and for ensuring data integrity and validity. Further details are available in the supplementary material.

LUNG SAFE enrolled patients with acute hypoxaemic respiratory failure admitted to a study ICU that underwent invasive or non-invasive ventilation. Exclusion criteria were age younger than 16 years or inability to obtain informed consent (where required). Patients were classified as having ARDS if they fulfilled all of the Berlin criteria [7]. We restricted subsequent analyses to patients that fulfilled ARDS criteria (93%) within 48 hours of the onset of acute hypoxemic respiratory failure (AHRF) and who received invasive mechanical ventilation (IMV) [Figure e1].

Data definitions

Our data definitions have been previously reported [7, 18, 19]. For the purposes of this analysis, sex assignment was made by the site investigators at the time of data entry. Lower tidal volume (LTV) ventilation was defined as a tidal volume of ≤ 8ml/kg ideal body weight (IBW). In patients in whom plateau pressure was measured, lung protective ventilation (LPV) was defined as tidal

volume of ≤ 8ml/kg IBW and a plateau pressure of ≤ 30 cmH_2O. From the variables originally collected we also derived dynamic compliance and body mass index (BMI). We used the threshold of 1.69 meters (median height value) to classify shorter versus taller patients. Gross domestic product (GDP) per person was obtained through World Bank database that gather time series data for all countries, on a variety of socio-economic topics. GDP was used to define three major geo-economic groupings: high-income countries in Europe, high-income countries in the rest of the world, and middle-income countries. Duration of IMV was calculated as the number of days between the date of intubation and the date of extubation in ICU (or death, if the patient died under IMV). Similarly, invasive ventilator-free days were calculated as the number of days from weaning from IMV to day 28, while patients who died before weaning were considered to have a ventilator-free-day value of 0. Length of stay (LOS) in ICU and in hospital was evaluated as the number of days between date of admission into the ICU and the date of discharge from ICU and hospital, respectively. Survival was evaluated at ICU and hospital discharge, or at day 90, whichever occurred first. Because we previously observed significant association between presence of ARDS at second day and outcomes [20], ARDS severity was reclassified ('resolved' versus 'confirmed' ARDS) on second day using the Berlin criteria.

Data management and statistical analyses

Descriptive statistics were reported for the study population stratified according to sex, and they included proportions for categorical and mean (standard deviation) or median (interquartile range) for continuous variables. No assumptions were made for missing data, which were rare. Comparisons between groups were performed using chi-squared test (or

Fisher exact test) for discrete variables, Student's t-test (or Wilcoxon-Mann Whitney test) for continuous variables. The Shapiro-Wilk test was used to assess normality in data distribution.

The Kaplan Meier approach was applied to assess the probability of discontinuing IMV in ICU, and the probability of hospital survival and of being discharged alive during hospital stay. When assessing the probability of discontinuing IMV in ICU, patients that weaned from IMV after 28 days in ICU are considered as censored at day 28. When assessing the probability of being discharged alive from hospital, patients that died before day 90 were considered as censored at date of death, while patients discharged after day 90 were considered as censored at day 90. Log-rank test was used to compare curves between the male and female population.

To evaluate the existence of a possible effect of sex on mortality, lower tidal volume ventilation during the first day of ARDS, LOS and on duration of IMV adjusting for all plausible confounders, we applied generalized linear mixed models with random intercept, taking into account the correlation among patients within the same ICU of enrolment. Patients died before ICU discharge were removed from analysis of LOS and duration of IMV. In detail, logistic link function and binomial distribution of outcome were used to analyse mortality and lower tidal volume ventilation, while log link function and Poisson distribution were used for LOS and for duration of IMV. In the first case, results were reported as odds ratio (OR) with 95% confidence interval (CI), while in the second as incidence rate ratio (IRR) and 95% CI. Because some ICUs had few observations to support the normal assumption, bootstrap method were used (1000 samples randomly extracted) to estimate the model parameters.

Predictors used in the multivariable models were detected through stepwise regression approach that combines forward and backward selection methods in an iterative procedure (significance level of 0.05 both for entry and retention). Potential independent predictors were: patient characteristics at baseline (age, sex, BMI, geo-economic area), chronic disease (chronic obstructive pulmonary disease (COPD), diabetes mellitus, immune-incompetence, cardiac failure, renal failure, liver failure), presence of ARDS risk factors, ICU's characteristics (number of beds, proportion of ICU beds in hospital, number of beds per physician and per nurse, academic ICU), clinical parameters measured at second day from ARDS onset (total respiratory rate, tidal volume, presence of controlled ventilation, positive end-expiratory pressure (PEEP), standardized minute ventilation, ARDS severity, dynamic compliance, partial pressure of carbon dioxide ($PaCO_2$), pH, non-pulmonary sequential organ failure assessment (SOFA) score, presence of adjunctive measures performed during two day from ARDS onset). Moreover, when sex was identified as a statistical significant predictor, we also evaluated its interaction with other selected predictors.

All p-values were two-sided, with p-values <0.05 considered as statistically significant.

Statistical analyses were performed with R, version 3.5.2. (R Project for Statistical Computing, http://www.R-project.org) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of the 12,906 patients enrolled in LUNG SAFE, 4,499 developed criteria for AHRF, 1,716 (38.1%) of whom were female, while 2,783 (61.9%) were male [Figure e1]. Identical proportions of females and males were observed in the study population of 2,377 patients who developed ARDS within two days from AHRF onset (ARDS D1-D2), and were managed with IMV [Figure e1]. The proportions of males and females aged 50 years or over were also unchanged in the study population [Table 1].

In the study population, female patients (n=905) were smaller and had higher BMI, and a greater frequency of immuno-incompetence (i.e. steroid use, cancer or haematological malignancies), while male patients (n=1,472) had a higher frequency of COPD and chronic renal failure [Table 1]. There were differences in risk factor profile, with gastric aspiration, major trauma, pulmonary contusion, and inhalation injury each less frequent in females [Table 1]. There was no difference in rates of clinician recognition of ARDS by sex.

There were no differences by sex in regard to the severity profile of ARDS or in overall severity of illness as defined by SOFA score on the first or second day of ARDS [Table 2, Table e1]. No statistically significant differences were observed between sexes in the progression of ARDS severity, whether in mild (p=0.2191), moderate (p=0.3575) or in severe (p=0.1613) patients on the second day [Figure e2]. There were no sex differences in inspired oxygen use, PaO_2/FiO_2 ratio or oxygen saturation on the first or second day.

The management of invasive MV differed by sex [Figure 1, Table 2, Table e1]. Tidal volumes were higher in females, both in those that received controlled or assisted mechanical

ventilation. Peak, plateau and driving pressures were higher, and standardized minute ventilation was higher, in females on the first and second day compared to males [Figure 1A-B, Table 2, Table e2]. In patients in whom plateau pressure was measured, more male patients received lung protective ventilation (75% versus 51%, $p < 0.0001$) [Figure 1C]. In contrast, there were no differences in PEEP levels used. $PaCO_2$ was lower and minute volume higher in females on first day of ARDS [Table 2], and a greater proportion of women were hypocapnic, while more men were hypercapnic [Table 2].

Tidal volumes sizes increased at lower height quintiles in both sexes [Figure 1D]. At the lowest quintile ($\leq$ 1.6 metres tall) where over 80% were female, tidal volume was significantly higher in females [Figure 1D]. Tidal volumes were higher in women at each quintile of actual body weight [Figure e3A]. LOESS regression demonstrated a clear relationship between lower height and higher tidal volume in women and men [***Figure e3B***]. At similar dynamic compliance, females received higher tidal volumes compared to males [***Figure e3C***]. Females continued to receive larger tidal volume sizes over each day of follow-up to day 14 [***Figure e3C, Table e3***]. More females received adjunctive measures (p=0.0322), with ECMO and inhaled vasodilators used more frequently in females compared to males [Table 2].

Multivariable models were constructed to examine factors associated with the use of lower tidal volume ventilation [***Table e4, Figure 1E***]. Factors including higher $PaCO_2$, controlled ventilation, higher pH and geo-economic area were associated with lower tidal volume use [***Table e6***]. In shorter patients (i.e. height ≤ median value of 1.69 meters), male sex was independently associated with use of lower tidal volume ventilation [***Figure 1E***].

There were differences in the recovery profile from ARDS between the sexes. Female patients had a shorter duration of IMV and reduced length of ICU and hospital stay compared to males [Table 3]. In surviving patients, female patients had more invasive ventilator-free days in ICU, a shorter duration of IMV, and reduced length of ICU and hospital stay compared to males [Table 3]. The overall probability of being discharged alive by day 90 was higher for female patients [Figure 2A].

Overall ICU and hospital mortality rates were identical for both females and males [Table 3]. Kaplan Meier analyses demonstrated no differences in the probability of discontinuing IMV or of hospital mortality during follow-up between sexes [Figure 2B-C]. There were no differences in limitation of life sustaining measure such as withdrawal or withholding of support between females and males [Table 3].

When patients were stratified by severity of ARDS on the second day, ICU mortality (64% versus 46%, p = 0.0066) and hospital mortality (68% versus 50%, p = 0.0068) were significantly higher for females who had severe 'confirmed' ARDS compared to males [Figure e4, Table e2]. Kaplan Meier analyses of hospital survival in male and female patients stratified by ARDS severity (at second day) demonstrated a significantly lower probability of survival in females with severe confirmed ARDS [Figure 3].

After adjusting for all potential confounders and considering the correlation among patients within the same ICU of enrolment, female sex was independently associated with reduced length of IMV, and a shorter ICU and hospital stay in survivors [Figure 4A, Table e5]. Female sex was associated with increased ICU and hospital mortality in patients with severe confirmed

ARDS [Figure 4B, Table e5]. Subsequent analysis of males and females with severe confirmed ARDS revealed no major differences in demographics or illness severity, but there were significant differences in ventilatory management between sexes [Table e6].

While there were geo-economic area differences in the in the use of low tidal volume ventilation [Table e4], and in overall outcomes of ARDS [Table e5, and e7] as previously reported [21], geo-economic area did not modify the relationships between sex and outcomes.

Discussion

Important sex based differences exist in the demographics, management and outcomes of patients with ARDS. There are differences in the demographics and risk factors for ARDS between females and males. Female patients are more likely to receive non-protective lung ventilation with higher tidal and minute volumes, and higher plateau and driving pressures compared to males. While this was due in part to their lower height profile, shorter females were more likely to receive lower tidal volume ventilation than shorter males. While female patients had a shorter duration of IMV and a reduced length of ICU and hospital stay, ICU and hospital mortality rates were identical compared to males. Of particular concern is the fact that female sex was independently associated with higher mortality in patients with severe confirmed ARDS.

Demographic differences are consistent with previous studies which found ARDS occurs more commonly in males than in females [10, 17]. We found no difference in age or clinician recognition of ARDS. Females with ARDS are shorter and have a higher BMI compared to males. Risk factors such as trauma, COPD and chronic renal failure were less common and immunosuppression more common in females, likely reflecting differences in smoking patterns, chronic kidney disease risk and cancer amongst females and males [22]. Sex hormone differences, such as estrogen and testosterone, can influence inflammation and immunological function [13, 14], which may impact on risk of developing ARDS. In pre-pubertal children, where hormone levels should be equally low between males and females, ARDS due to non-septic causes occurs equally. However, ARDS secondary to sepsis occurs in a greater frequency in male children suggesting a biological reason for difference in risks for ARDS where hormonal levels

between males and females are equal [14]. In this analysis, in patients aged over 50 there was no increase in the proportion of females to males, suggesting that the frequency of ARDS does not increase in females post menopause.

We next assessed if ventilatory management of ARDS differs between male and female patients with ARDS. A higher proportion of females received non-protective lung ventilation, and a greater proportion were hypocapnic. These differences in ventilation in females persisted out to day 14, suggesting this was sustained over time. If actual rather than ideal body weight is used to calculate the delivered tidal volume, the tidal volume may be inappropriately high [10]. Interestingly, at each quintile of actual body weight, females received significantly higher tidal volumes, while weight was not associated with low tidal volume use. We found that, in shorter patients, both female and male, clinicians were less likely to apply lower tidal volumes ventilation, confirming and expanding prior findings [10]. While the delivery of higher tidal volumes to females patients has been previously described [23], this has been attributed solely to their (shorter) height [10, 23]. Our findings show that female sex is a factor, with shorter females significantly less likely than similarly sized males to receive lower tidal volume ventilation.

Mortality in females may have been lower if LPV had been appropriately used. Understanding the barriers to LPV implementation is important [10, 24, 25]. LPV is associated with an 8.8% reduction in mortality in one study, with another finding that for each 1ml/kg increase in initial tidal volume above predicted body weight being associated with a 23% increase in mortality [26]. Overall, females are shorter than males and height measurement errors are magnified in shorter individuals, particularly where height is estimated [12]. In individuals undergoing

abdominal surgery >4 hours of duration, female sex, short stature and obesity were associated with use of tidal volume > 10ml/kg [27]. The greater risk of shorter females receiving inappropriately high tidal volumes highlights the need for particular care and attention in calculating and applying lower tidal volumes to this cohort.

There were important differences in the recovery profile and in outcomes between the sexes. Females with ARDS required shorter ICU stays, and had more ventilator-free days. This did not appear to be a 'survivor bias' as this finding persisted in surviving patients. Despite this, overall ICU and hospital mortality was identical in females and males with ARDS. Prior studies have reported similar findings, with female patients with critical illnesses including acute lung injury having shorter ICU stays and requiring less resource use [6, 15, 17, 28, 29], but with similar mortality rates to their male counterparts. There are preclinical and clinical data to suggest that women and men respond differently to inflammation [30], and to mechanical ventilation [17]. In one study, mechanically ventilated women had a faster alveolar fluid clearance rate compared to men [31]. These findings raise the possibility that women may recover from ARDS faster than men, but that this may be nullified by the lower rates of lung protective ventilation in women. Additional studies are required to further examine these issues.

Our findings regarding outcomes from ARDS provide important additional insights compared with prior studies. Our finding of no overall differences in outcome from ARDS by sex, confirms prior findings in a meta-analysis of outcomes from the ARDSnet studies [32]. Other studies have noted worse outcomes for females on mechanical ventilation but with organ dysfunction explaining most of the differences [33]. We examined outcomes by day 2 severity, as we have previously demonstrated that reclassification at day 2 provides additional insights [20]. The

finding that female patients with severe confirmed ARDS had increased mortality is a novel finding, and is of concern. Differences in risk factor profile (e.g. greater pneumonia and non-pulmonary sepsis, lower trauma) may explain some of the outcome differences in the sexes, but overall these differences were relatively small. There were relatively little differences in illness severity profiles between males and females with severe confirmed ARDS. However, females with severe ARDS did received higher tidal volumes, and were exposed to higher airway pressures, compared to males with severe ARDS, which is of concern given their worse outcome compared to their male counterparts. In this study, females were not more likely to receive orders relating to limitation of life sustaining therapies following ICU admission, which is consistent with other studies [34, 35].

As previously reported, differences exist in the management of patients with ARDS based on geo-economic region [36]. Differences in outcomes related to geo-economic region were noted, with ICU and hospital mortality lowest in high income countries. However, geo-economic difference was not a factor in modifying the relationship between sex and mortality. The proportion of patients with severe ARDS was lower whilst use of LPV was higher in non-European high income countries which might explain the lowest proportion of female patients dying from ARDS in these countries compared to other geo-economic areas [36]. It is reassuring that no sex based differences in access to care for patients with ARDS was found in the study.

This study has several limitations related to study design, as have been previously described.[7] Limitations pertaining to this study include the possibility that all females with ARDS were not accounted for, i.e. due to non-admission and palliation outside of the ICU. Associations of management with worse outcomes in females with severe ARDS were examined only for D1

and D2 of ARDS. However, early management of ARDS is important to outcome, and choosing a longer time point to analyse would have decreased patient numbers due to ICU discharges or patient death.

In conclusion, higher proportions of shorter females with ARDS receive non-protective lung ventilation compared to similarly sized males. There appear to be differences in recovery profiles between the sexes, with females requiring shorter ICU stays, and more ventilator-free days. Of concern, females with severe confirmed ARDS have a higher mortality compared to their male counterparts. These findings suggest that females with ARDS require particular attention their ventilatory management in order to optimise their outcomes.

Table 1. Characteristics of female and male patients with ARDS invasively ventilated (n=2,377).

	Female	Male	p-value [1]
Number of patients (%)	905 (38.1)	1,472 (61.9)	
Number of patients > 50 years (%)	665 (37.2)	1,123 (62.8)	
Age (years), mean ± SD	60.1 ± 17.3	60.8 ± 16.5	0.4057
Height (m), mean ± SD	1.60 ± 0.08	1.73 ± 0.08	<0.0001
BMI (kg/m^2), mean ± SD	28.8 ± 9.2	26.8 ± 8.4	<0.001
Chronic disease, n (%):			
COPD	157 (17.3)	315 (21.4)	0.0162
Diabetes mellitus	195 (21.5)	320 (21.7)	0.9121
Immuno-incompetence (all types)	205 (22.7)	280 (19.0)	0.0330
Chronic cardiac failure	82 (9.1)	142 (9.6)	0.6349
Chronic renal failure	71 (7.8)	153 (10.4)	0.0389
Chronic liver failure	32 (3.5)	71 (4.8)	0.1344
Risk factor for ARDS [2], n (%):			
Pneumonia	541 (59.8)	844 (57.3)	0.2410
Non-pulmonary sepsis	170 (18.8)	243 (16.5)	0.1549
Aspiration of gastric contents	116 (12.8)	256 (17.4)	0.0029
Non-cardiogenic shock	84 (9.3)	115 (7.8)	0.2092
Major trauma	22 (2.4)	85 (5.8)	0.0001
Blood transfusion	44 (4.9)	59 (4.0)	0.3209
Pulmonary contusion	18 (2.0)	62 (4.2)	0.0035
Inhalation injury	17 (1.9)	51 (3.5)	0.0243
Drug overdose	14 (1.5)	35 (2.4)	0.1663
Pulmonary vasculitis	2 (0.2)	7 (0.5)	0.4966
Severe burns	4 (0.4)	4 (0.3)	0.4890
Drowning	0 (0.0)	2 (0.1)	0.5283
Pancreatitis	13 (1.4)	37 (2.5)	0.0756
Other	30 (3.3)	39 (2.6)	0.2481
Risk factor for ARDS, n (%):			0.2625
Only pulmonary risk factors	511 (56.6)	843 (57.3)	
Only non-pulmonary risk factors	196 (21.7)	286 (19.4)	
Both	126 (13.9)	239 (16.2)	
No risk factor	72 (8.0)	104 (7.1)	
Type of admission, n (%)			
Medical	692 (76.5)	1,073 (72.9)	0.0532
Postoperative (elective)	55 (6.1)	88 (6.0)	0.9214
Surgical	136 (15.0)	230 (15.6)	0.6952

Trauma	22 (2.4)	81 (5.5)	0.0004
Clinician recognition of ARDS, n (%)			
At baseline	300 (33.1)	486 (33.0)	0.9467
During ICU stay	592 (65.4)	938 (63.7)	0.4031
ICU characteristics			
Number of beds, median [IQR]	17.0 [11.0 ; 24.0]	17.0 [11.0 ; 25.0]	0.6169
Proportion of bed in hospital, median [IQR]	2.5 [1.5 ; 4.5]	2.6 [1.5 ; 4.4]	0.4057
Bed per physician, median [IQR]	5.0 [2.7 ; 10.0]	4.8 [2.7 ; 9.4]	0.3759
Bed per nurse, median [IQR]	1.4 [1.0 ; 2.0]	1.4 [1.0 ; 2.0]	0.9712
Academic, n (%)	687 (78.4)	1,083 (76.1)	0.1897

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; SD: Standard Deviation.

1 Comparison of male versus female patients.

2 Total is greater than 100%, since patients could have more than one risk factor.

Table 2. Ventilatory management and illness severity of female and male patients (n=2,377).

	Female (n = 905)	Male (n = 1,472)	p-value [0]
Invasive ventilation settings at ARDS onset (1st day)			
Patients undergoing controlled ventilation, n (%)	631 (70.6)	980 (68.1)	0.1995
Set respiratory rate (breaths/min), mean ± SD	18.5 ± 6.1	18.7 ± 10.0	0.9509
Total respiratory rate (breaths/min), mean ± SD	20.6 ± 6.4	20.9 ± 9.7	0.7230
Tidal volume (ml/kg IBW), mean ± SD			
All patients	8.2 ± 2.1	7.2 ± 1.6	<0.0001
Patients with control ventilation	8.0 ± 2.0	7.1 ± 1.5	<0.0001
Patients with spontaneous ventilation	8.6 ± 2.2	7.5 ± 1.8	<0.0001
P-value (control vs spontaneous ventilation)	0.0005	0.0003	
Lower tidal volume [1], n (%)	424 (49.6)	1,039 (74.2)	<0.0001
Set PEEP (cmH_2O), mean ± SD	8.5 ± 3.4	8.4 ± 3.3	0.9046
Peak pressure [2] (cmH_2O), mean ± SD	28.0 ± 8.6	26.5 ± 7.9	<0.0001
Dynamic compliance (ml/cmH_2O), mean ± SD	27.31 ± 22.83	34.65 ± 32.61	<.0001
Patients in whom P_{PLAT} measured, n (%)	371 (41.0)	583 (39.6)	0.5025
P_{PLAT} (cmH_2O) [3] , mean ±SD	24.1 ± 6.0	22.6 ± 6.1	0.0003
Driving pressure (cmH_2O) [3] , mean ± SD	15.7 ± 5.6	14.1 ± 5.4	0.0001
Standardized minute ventilation (l/min) [4] , mean ± SD	9.61 ± 4.4	11.53 ± 5.1	0.0001
Standardized minute ventilation (l/min/Kg IBW) [4] , mean ± SD	0.18 ± 0.09	0.17 ± 0.07	<0.0001
Gas exchange (1st day)			
P_aO_2 / FiO_2 (mmHg), mean ± SD	162.1 ± 68.7	159.6 ± 67.5	0.4261
SpO_2 , median [IQR]	96.0 [93.0 ; 98.0]	96.0 [93.0 ; 98.0]	0.9153
P_aCO_2 (mmHg), mean ± SD	45.2 ± 15.5	46.5 ± 14.6	0.0008
<35, n (%)	190 (21.3)	244 (16.7)	0.0061
35 – 45, n (%)	341 (38.1)	535 (36.7)	0.4804
≥ 45, n (%)	363 (40.6)	679 (46.6)	0.0047
pH , mean ± SD	7.32 ± 0.13	7.33 ± 0.12	0.8145
Severity profile (1st day)			
ARDS severity, n (%)			0.8743
Mild, n (%)	275 (30.4)	439 (29.8)	
Moderate, n (%)	423 (46.7)	683 (46.4)	
Severe, n (%)	207 (22.9)	350 (23.8)	
SOFA score [5], mean ± SD	9.9 ± 4.0	10.1 ± 4.0	0.1713
Non pulmonary SOFA score [5], mean ± SD	6.7 ± 4.0	6.9 ± 3.9	0.2266
FiO_2, median [IQR]	0.6 [0.5 ; 0.9]	0.6 [0.5 ; 0.9]	0.7265
Adjunctive measures (first 48 hours)			
Neuromuscular blockade	160 (17.7)	245 (16.6)	0.5144

Recruitment maneuvers	173 (19.1)	251 (17.1)	0.2017
Prone positioning	48 (5.3)	65 (4.4)	0.3231
ECMO	36 (4.0)	27 (1.8)	0.0016
Inhaled vasodilators	62 (6.9)	65 (4.4)	0.0104
HFOV	1 (0.1)	5 (0.3)	0.4175
None of the above	578 (63.9)	1,003 (68.1)	0.0322

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; ECMO: Extra Corporeal Membrane Oxygenation; FiO_2: Fraction of Inspired oxygen; HFOV: High Frequency Oscillatory Ventilation; IBW: Ideal Body Weight; IQR: interquartile range (1^{st} quartile and 3^{rd} quartile); P_aCO_2 partial pressure of carbon dioxide; P_aO_2: arterial oxygen partial pressure; PEEP: Positive End-Expiratory Pressure; P_{PLAT}: Plateau Pressure; SD: Standard Deviation; SOFA: Sequential Organ Failure Assessment; SpO_2: peripheral oxygen saturation.

0. Comparison of male versus female patients.

1. Lower tidal volume was defined as tidal volume $\leq$ 8 ml/kg IBW.

2. For peak pressure measurements patients receiving HFOV or ECMO were excluded.

3. P_{PLAT} and driving pressure values are limited to patients in whom this value was reported, and in whom either an assist control mode was used or, where a mode permitting spontaneous ventilation was used, the set and total respiratory rates were equal. Patients receiving HFOV or ECMO were also excluded.

4. Standardized minute ventilation was calculated as minute ventilation $\times$ P_aCO_2 / 40.

5. For all SOFA scores, where data points were missing, this value was omitted and the denominator adjusted accordingly.

6. At day 2, ARDS severity profile was evaluable for 788 females (90.5% on females in ICU at day 2) and for 1,326 males (92.9% on males in ICU at day 2).

Table 3. Outcomes observed during follow-up in invasively ventilated female and male patients with ARDS (n=2,377).

	Female (n = 905)	Male (n = 1,472)	p-value [1]
Ventilatory support at ICU discharge, n (%)			
All patients	232 (25.64)	351 (23.85)	0.3246
Survivors at ICU discharge	118 (20.17)	162 (16.98)	0.1154
Invasive ventilator-free days (days)[2] in ICU, median [IQR]			
All patients	13.0 [0.0 ; 23]	10.5 [0.0 ; 22.0]	0.1616
Survivors at ICU discharge	22.0 [16.0 ; 25.0]	20.0 [13.0 ; 25.0]	0.0134
Duration of invasive mechanical ventilation (days) [3] in ICU, median [IQR]			
All patients	7.0 [4.0 ; 13.0]	9.0 [4.0 ; 16.0]	0.0044
Survivors at ICU discharge	7.0 [4.0 ; 13.0]	9.0 [4.0 ; 16.0]	0.0124
Length of stay in ICU (days) [4], median [IQR]			
All patients	9.0 [5.0 ; 17.0]	11.0 [6.0 ; 20.0]	0.0014
Survivors at ICU discharge	11.0 [6.0 ; 18.0]	12.0 [7.0 ; 22.0]	0.0094
Length of stay in hospital (days) [5], median [IQR]			
All patients	16.0 [8.0 ; 29.0]	18.0 [9.0 ; 35.0]	0.0006
Survivors at hospital discharge	21.0 [13.0 ; 36.0]	25.0 [14.0 ; 44.0]	0.0012
Limitation of life sustaining measures in ICU, n (%)			
All patients	225 (24.9)	353 (24.0)	0.6269
Patients die in ICU after limitation [6]	179 (79.6)	285 (80.7)	0.7279
Time to limitation in ICU, mean ± SE [7]	50.5 ± 3.1	54.7 ± 1.9	0.0834
ICU mortality, n (%)			
All patients	320 (35.4)	518 (35.2)	0.9333
Patients in European high income countries	184 (39.6)	277 (34.7)	0.0837
Patients in non-European high income countries	59 (23.3)	122 (30.8)	0.0380
Patients in middle income countries	77 (41.2)	119 (42.8)	0.7272
P-value (among geo-economic regions)	<.0001	0.0053	
Hospital mortality [8], n (%)			
All patients	362 (40.2)	590 (40.2)	0.9844
Patients in European high income countries	212 (45.7)	315 (39.5)	0.0309
Patients in non-European high income countries	69 (27.4)	147 (37.3)	0.0091
Patients in middle income countries	81 (43.8)	128 (46.5)	0.5597
P-value (among geo-economic regions)	<.0001	0.0462	

Abbreviations: ICU: Intensive Care Unit; IQR: interquartile range (1st quartile; 3rd quartile). SE: standard error.

1. Comparison of male versus female patients.

2. Invasive ventilator-free days were calculated as the number of days from weaning from invasive mechanical ventilation to the date of ICU discharge. Patients who died before weaning were considered to have a ventilator-free-day value of 0.

3. Duration of invasive mechanical ventilation was assessed during ICU stay and it was calculated as the number of days between the date of intubation and the date of extubation performed in ICU.

4. Length of stay in ICU was calculated as the number of days between the date of ICU admission and the date of ICU discharge (or 90 when discharge occurred after 90 days).
5. Length of stay in hospital was calculated as the number of days between the date of ICU admission and the date of hospital discharge (or 90 when discharge occurred after 90 days).
6. Percentage is calculated on patients with limitation of life sustaining measures.
7. Mean time to limitation of life sustaining measures in ICU was estimated with Kaplan-Meier approach, considering as censored those patients discharged from ICU.
8. Vital status at hospital discharge was not evaluable for 9 patients (4 females and 5 males).

FIGURE AND TABLE LEGENDS

Figure 1. Impact of sex on ventilatory parameters at first day of ARDS in invasively ventilated patients.

Panel A. Cumulative frequency distribution of tidal volume in males (n=445) and females (n=278).

Panel B. Cumulative frequency distribution of plateau pressure in males (n=445) and females (n=278).

Note: Data are limited to patients with available plateau pressure, and in whom either an assist control mode was used or, where a mode permitting spontaneous ventilation was used, the set and total respiratory rates were equal. Patients receiving HFOV or ECMO were also excluded.

Panel C. Distribution of tidal volume and plateau pressure in males (n=445) and females (n=278) by ARDS severity at onset.

Note1: Data are limited to patients with available plateau pressure, and in whom either an assist control mode was used or, where a mode permitting spontaneous ventilation was used, the set and total respiratory rates were equal. Patients receiving HFOV or ECMO were also excluded.

Note2: P-value refers to comparison with female patients.

Panel D. Boxplot for tidal volume (ml/ kg IBW) in male and female population stratified by quintiles of height in study population.

Note1: * refers to p-value < 0.05 for the comparison between females and males.

Note2: Pearson correlation coefficient between tidal volume and height in females and males is -0.3439 ($p<0.0001$) and -0.2855 ($p<0.0001$), respectively.

Panel E. Odds Ratios (and 95% CI) for receiving lower tidal volume ventilation (tidal volume $\leq$ 8 ml/kg IBW) of males versus females.

Figure 2. Kaplan-Meier curves for main outcomes in ARDS patients invasively ventilated, stratified by sex.

Note: the number of patients at risk reported in the bottom of figure is referred to the end of corresponding day.

Panel A. Probability of being discharged alive from hospital.

Note: patients discharged alive/dead after day 90 and dead patients are considered as censored at day 90 or at date of death, respectively.

Panel B. Probability of discontinuing invasive mechanical ventilation (IMV) in ICU.

Note: patients with weaning from IMV after 28 days in ICU are consider as censored at day 28.

Panel C. Probability of hospital survival.

Note: patients discharged alive before day 90 are considered alive at day 90.

Figure 3. Probability of hospital survival in male and female patients stratified by ARDS severity at second day.

Note1: the number of patients at risk reported in the bottom of figure is referred to the end of corresponding day.

Note2: patients discharged alive before day 90 are considered alive at day 90.

Panel A. Patients with resolved ARDS.

Panel B. Patients with mild ARDS.

Panel C. Patients with moderate ARDS.

Panel D. Patients with severe ARDS.

Figure 4. Effects of sex on main outcomes in patients with ARDS.

Panel A. Incidence Rate Ratio (IRR) of males versus females for length of stay in ICU, in hospital and for duration of invasive mechanical ventilation (IMV).

Panel B. Odds ratios (OR) for ICU and hospital mortality of males versus females, by ARDS severity at second day (resolved, mild, moderate and severe).

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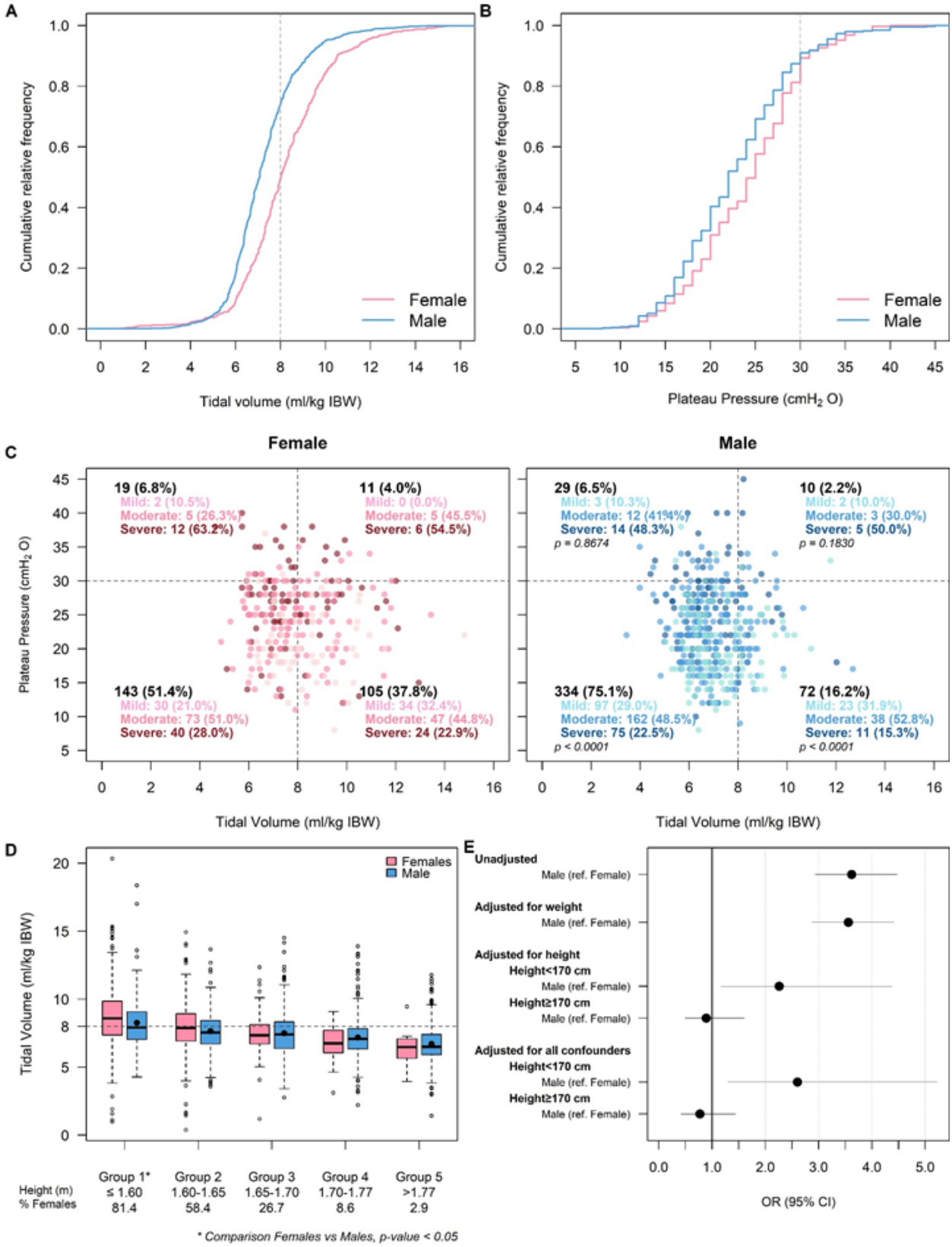
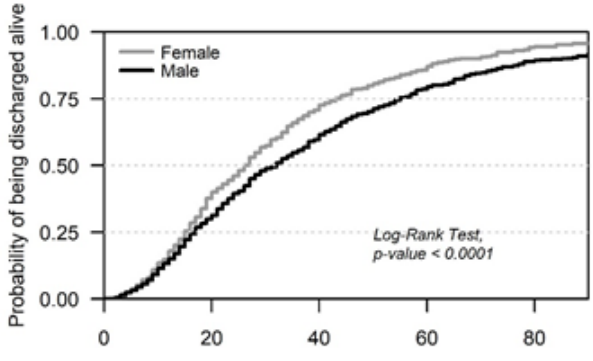
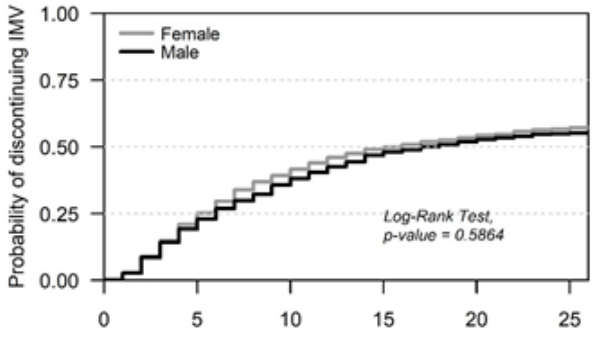

A
Cumulative relative frequency
Tidal volume (ml/kg IBW)
Female
Male
B
Cumulative relative frequency
Plateau Pressure (cmH2 O)
Female
Male
C
Female
Male
Plateau Pressure (cmH2 O)
19 (6.8%)
Mild: 2 (10.5%)
Moderate: 5 (26.3%)
Severe: 12 (63.2%)
11 (4.0%)
Mild: 0 (0.0%)
Moderate: 5 (45.5%)
Severe: 6 (54.5%)
143 (51.4%)
Mild: 30 (21.0%)
Moderate: 73 (51.0%)
Severe: 40 (28.0%)
105 (37.8%)
Mild: 34 (32.4%)
Moderate: 47 (44.8%)
Severe: 24 (22.9%)
29 (6.5%)
Mild: 3 (10.3%)
Moderate: 12 (41.4%)
Severe: 14 (48.3%)
p = 0.8674
10 (2.2%)
Mild: 2 (10.0%)
Moderate: 3 (30.0%)
Severe: 5 (50.0%)
p = 0.1830
334 (75.1%)
Mild: 97 (29.0%)
Moderate: 162 (48.5%)
Severe: 75 (22.5%)
p < 0.0001
72 (16.2%)
Mild: 23 (31.9%)
Moderate: 38 (52.8%)
Severe: 11 (15.3%)
p < 0.0001
Tidal Volume (ml/kg IBW)
Tidal Volume (ml/kg IBW)
D
Females
Male
Tidal Volume (ml/kg IBW)
Height (m)
% Females
Group 1* ≤ 1.60 81.4
Group 2 1.60-1.65 58.4
Group 3 1.65-1.70 26.7
Group 4 1.70-1.77 8.6
Group 5 >1.77 2.9
* Comparison Females vs Males, p-value < 0.05
E
Unadjusted
Male (ref. Female)
Adjusted for weight
Male (ref. Female)
Adjusted for height
Height<170 cm
Male (ref. Female)
Height≥170 cm
Male (ref. Female)
Adjusted for all confounders
Height<170 cm
Male (ref. Female)
Height≥170 cm
Male (ref. Female)
OR (95% CI)

A



# at risk					
Female	885	352	131	55	18
Male	1435	674	307	139	61

B



# at risk						
Female	888	703	540	452	414	385
Male	1447	1170	932	771	698	653

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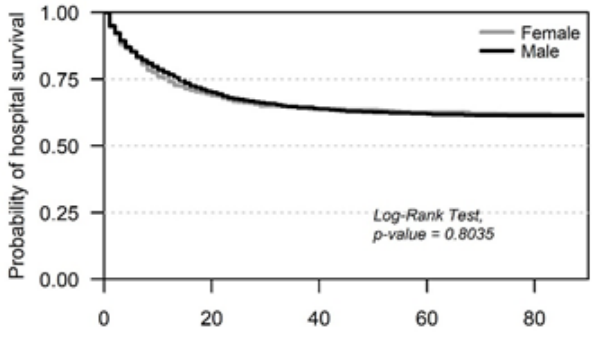

# at risk					
Female	873	606	556	547	541
Male	1432	1008	915	890	877

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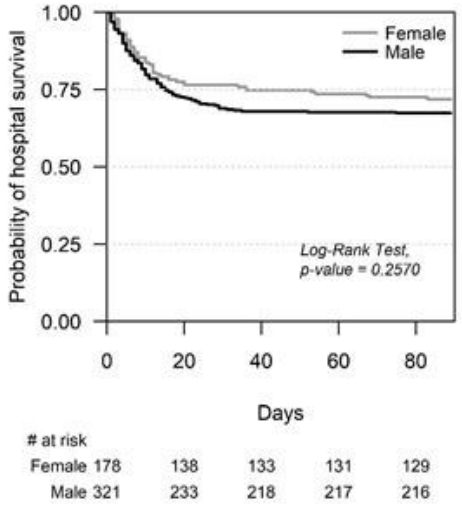
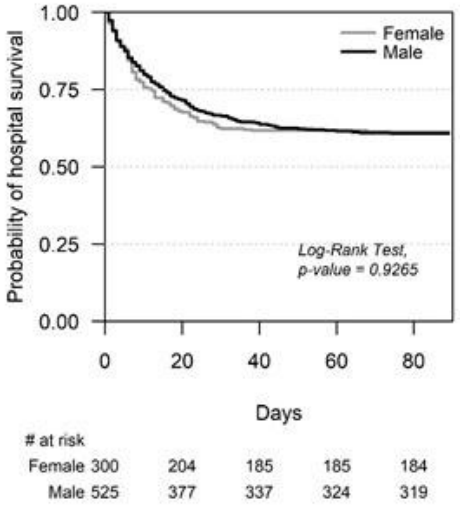


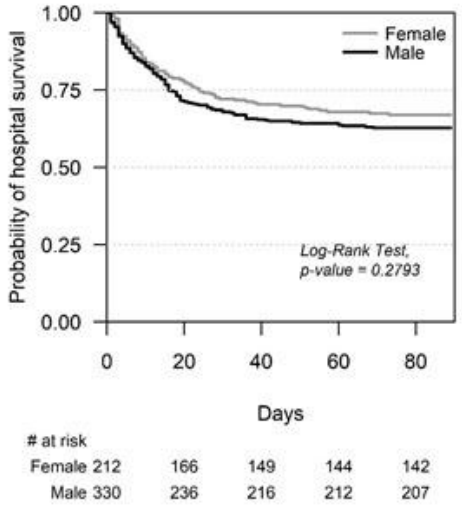
# at risk					
Female	178	138	133	131	129
Male	321	233	218	217	216

C



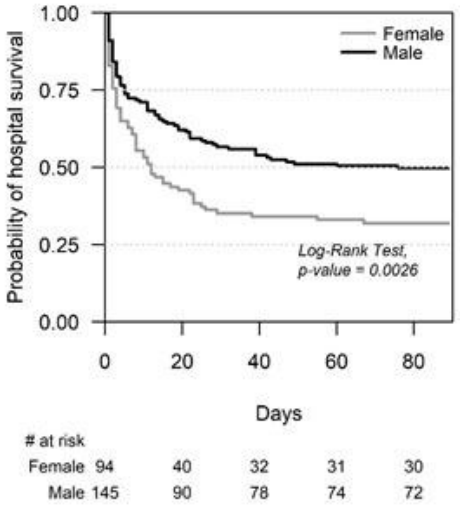
# at risk					
Female	300	204	185	185	184
Male	525	377	337	324	319

B

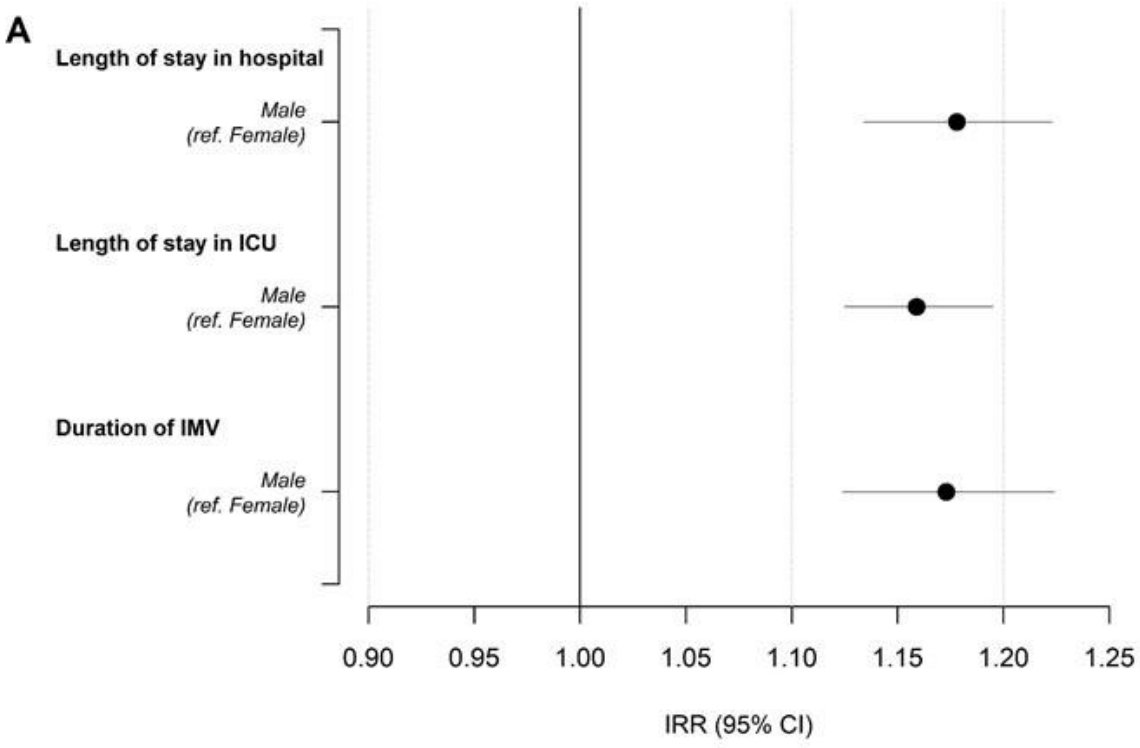


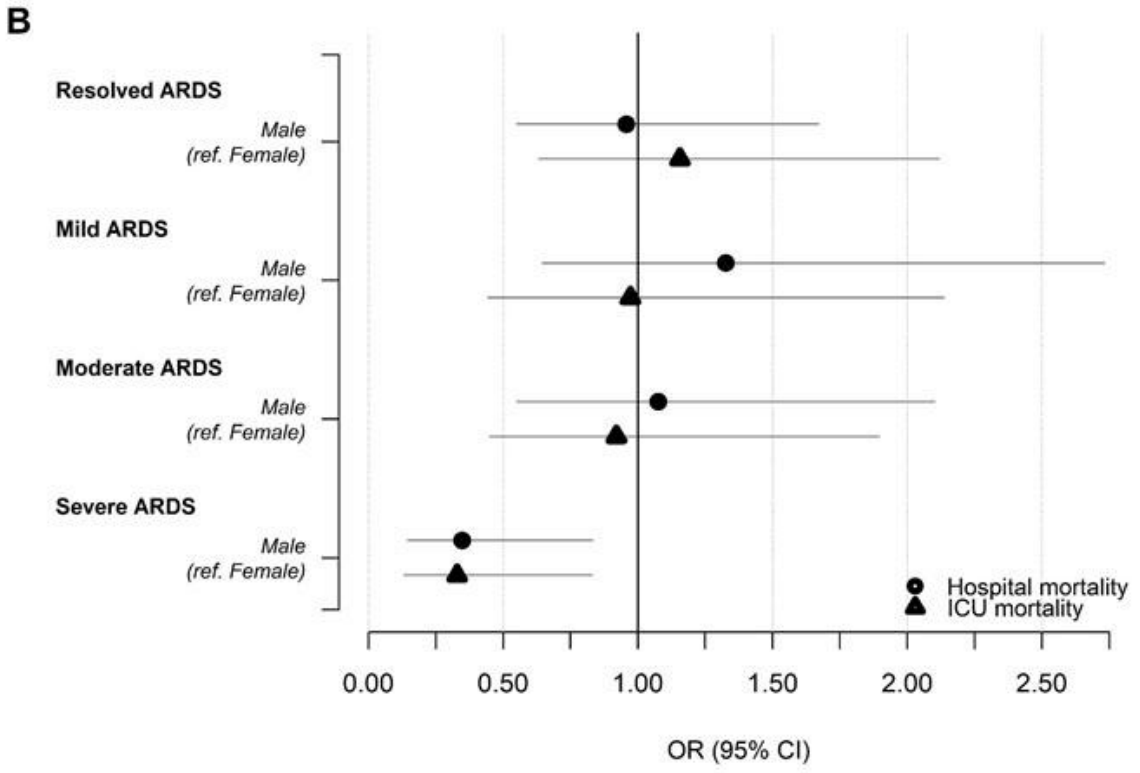
# at risk					
Female	212	166	149	144	142
Male	330	236	216	212	207

D



# at risk					
Female	94	40	32	31	30
Male	145	90	78	74	72


A
Length of stay in hospital
Male
(ref. Female)
Length of stay in ICU
Male
(ref. Female)
Duration of IMV
Male
(ref. Female)
0.90
0.95
1.00
1.05
1.10
1.15
1.20
1.25
IRR (95% CI)


B
Resolved ARDS
Male
(ref. Female)
Mild ARDS
Male
(ref. Female)
Moderate ARDS
Male
(ref. Female)
Severe ARDS
Male
(ref. Female)
Hospital mortality
ICU mortality
0.00
0.50
1.00
1.50
2.00
2.50
OR (95% CI)

Title: Differences in the demographics, management and outcome of women and men with Acute Respiratory Distress Syndrome in the LUNG SAFE prospective cohort study.

Authors: *B.A. McNicholas, *F Madotto, T Pham, E Rezoagli, C.H. Masterson, S Horie, G Bellani, L. Brochard, J.G. Laffey. On behalf of the LUNG SAFE Investigators and the ESICM Trials Group.

ONLINE DATA SUPPLEMENT

Expanded Methods and Materials

Study Design

LUNG SAFE (ClinicalTrials.gov NCT02010073) was a prospective, observational, international multi-centre cohort study. Enrollment took place over four consecutive winter weeks (February-March in the northern hemisphere and June-August 2014 in the southern hemisphere), as selected by each participating site. The study, conceived by the Acute Respiratory Failure Section of 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 and/or site investigators (see below, ***Appendix 1)*** were responsible for obtaining ethics' approval where required, data integrity and validity. Data were collected by means of an electronic case report form (eCRF, Clinfile®, Paris, France). Data quality was subsequently verified on the database and investigators were queried in regard to outlier or inconsistent data. National coordinators (***Appendix 1***) and site investigators (***Appendix 1***) were responsible for obtaining ethics committee approval and for ensuring data integrity and

validity. Full methods are described in detail in the primary study paper [1] and in subsequent papers [2, 3].

Patients, Study Design and Data Collection

Investigators were requested to enroll all patients admitted to their Intensive Care Unit (ICU) within the 4-week enrollment window and receiving invasive mechanical ventilation (MV) or NIV. As previously described [1], exclusion criteria were: age<16 years or inability to obtain informed consent, where required. Following enrollment, patients were evaluated daily for Acute Hypoxemic Respiratory Failure (AHRF), defined as the concurrent presence of: (1) $PaO_2/FiO_2 \leq 300$ mmHg; (2) new pulmonary parenchymal abnormalities on chest X-Ray or computed tomography; and (3) ventilatory support with continuous positive airway pressure (CPAP) or expiratory positive airway pressure (EPAP) or positive end expiratory pressure (PEEP) ≥5 cmH_2O. At this stage, for patients fulfilling criteria for AHRF a more detailed set of data was recorded, which allowed us to determine whether or not the patient fulfilled the Berlin criteria for ARDS.

Data on arterial blood gases, type of ventilatory support with relative settings and Sequential Organ Failure Assessment (SOFA) score were collected on selected days during the ICU stay. Data were collected once per day: if more than one value was available during the day, investigator were asked to record data collected as close as possible to 10 AM. Data on ventilatory settings were recorded simultaneously with arterial blood gas. Decisions to withhold or withdraw life sustaining treatments during the ICU stay and the time at which this decision was taken were recorded (all-time treatment limitations). ICU and hospital survival were collected at the time of discharge, censored at 90 days after enrollment (whichever occurred

earlier). Hence, in the manuscript, ICU- and hospital survival indicate the respective values censored at 90 days.

Consistent with our previous reports, we restricted subsequent analyses to patients that fulfilled ARDS criteria (93%) within 48 hours of the onset of acute hypoxemic respiratory failure (AHRF) and who received invasive mechanical ventilation (IMV) [Figure e1].

Data Definitions

The electronic version of the CRF (eCRF) provided a detailed explanation of what was meant by the term "lung fields abnormal", which included the stipulation for bilateral airspace disease and the fact that atelectasis or effusion should be excluded. In addition, the site investigators received training using an electronic module in the diagnosis of ARDS and had to differentially diagnose ARDS from other common causes of parenchymal lung radiologic changes including heart failure from a clinical summary and the CXR.

For the purposes of this analysis, sex assignment was made by the site investigators at the time of data entry. Lower tidal volume ventilation was defined as a tidal volume of ≤ 8ml/kg PBW. In patients in whom plateau pressure was measured, lung protective ventilation (LPV) was defined as tidal volume of ≤ 8ml/kg ideal body weight (IBW) PBW combined with a plateau pressure of ≤ 30 cmH_2O. From the variables originally collected we also derived: 1) dynamic compliance (ml/cmH_2O) as the ratio between tidal volume and the difference between peak inspiratory pressure and PEEP; 2) body mass index (BMI) as the ratio between weight (kilograms) and the square of the body height (metres). We used the threshold of 1.69 meters (median height value) to classify shorter versus taller patients. Gross domestic product (GDP) per person was obtained through World Bank database that gather time series data for all countries, on a variety of socio-economic topics. GDP was used to define three major geo-economic groupings: high-income countries in Europe, high-income countries in the rest of the world, and middle-income countries.

Duration of IMV was calculated as the number of days between the date of intubation and the date of extubation in ICU (or death, if the patient died under IMV). Similarly, invasive ventilator-free days were calculated as the number of days from weaning from IMV to day 28, while

patients who died before weaning were considered to have a ventilator-free-day value of 0. Length of stay (LOS) in ICU and in hospital was evaluated as the number of days between date of admission into the ICU and the date of discharge from ICU and hospital, respectively. Driving pressure was defined as plateau pressure minus PEEP. Plateau and driving pressure analysis confined to patients (n=742) in whom plateau pressure was measured and in whom there was no evidence of spontaneous ventilation (i.e. when set and measured respiratory rates were equal). All modes other than volume and pressure control modes were considered to permit spontaneous breathing.

Because we previously observed significant association between presence of ARDS at second day and outcomes [4], ARDS severity was reclassified ('resolved' versus 'confirmed' ARDS) on second day using the Berlin criteria. In detail, patients were considered to have 'resolved' ARDS when they initially fulfilled the Berlin ARDS criteria but did not fulfill at least one criterion on day 2. Patients were considered to have 'confirmed' ARDS when they continued to fulfill the Berlin definition when reassessed on day 2. Where chest radiography was not present at day 2, patients could only be considered to have confirmed ARDS if the other criteria were still present. Where data on PEEP were missing at day 2, patients were considered to have confirmed ARDS if: (a) the other criteria were fulfilled, and (b) there were data on the third day indicating ongoing assisted ventilation with a PEEP of 5 cmH_2O or greater. Patients could not be deemed to have resolved ARDS if any of the day 2 data was missing.

Quality control

At the time of data entry, the site investigators were required to answer all queries raised by the case report form before they could electronically finalize a patient dataset. Patient datasets

that were not finalized were not included in the analysis. In addition, prior to analysis, all data were screened for potentially erroneous data and outliers; these data were verified/corrected by LUNG-SAFE site investigators. We followed the STROBE (Strengthening The Reporting of OBservational studies in Epidemiology) statement guidelines for observational cohort studies [5].

Study size

We wished to enroll at least 1000 patients with ARDS. Assuming a 30% mortality, 300 deaths would allow us to evaluate at least 30 associated variables in multivariable models [6]. Prior epidemiologic studies reported an ARDS incidence ranging between 2.2-19% of ICU patients [7-10]. Based on a conservative a priori estimate that 5% of ICU admissions would have ARDS, and projecting that a medium-sized ICU admits 50 patients per month, we planned to enroll at least 500 ICUs world-wide.

Data Management and Statistical Analyses

Descriptive statistics were reported for the study population stratified according to sex, and they included proportions for categorical and mean (standard deviation) or median (interquartile range) for continuous variables. No assumptions were made for missing data, which were rare. Comparisons between groups were performed using chi-squared test (or Fisher exact test) for discrete variables, Student's t-test (or Wilcoxon-Mann Whitney test) for continuous variables. The Shapiro-Wilk test was used to assess normality in data distribution.

The Kaplan Meier approach was applied to assess the probability of discontinuing IMV in ICU, and the probability of hospital survival and of being discharged alive during hospital stay. When

assessing the probability of discontinuing IMV in ICU, patients that weaned from IMV after 28 days in ICU are considered as censored at day 28. When assessing the probability of being discharged alive from hospital, patients that died before day 90 were considered as censored at date of death, while patients discharged after day 90 were considered as censored at day 90. Log-rank test was used to compare curves between the male and female population.

To evaluate the existence of a possible effect of sex on mortality, lower tidal volume ventilation (tidal volume ≤ 8 ml/kg of ideal body weight) during the first day of ARDS, LOS and on duration of IMV adjusting for all plausible confounders, we applied generalized linear mixed models with random intercept, taking into account the correlation among patients within the same ICU of enrolment. Patients died before ICU discharge were removed from analysis of LOS and duration of IMV. In detail, logistic link function and binomial distribution of outcome were used to analyse mortality and lower tidal volume ventilation, while log link function and Poisson distribution were used for LOS and for duration of IMV. In the first case, results were reported as odds ratio (OR) with 95% confidence interval (CI), while in the second as incidence rate ratio (IRR) and 95% CI. Because some ICUs had few observations to support the normal assumption, bootstrap method were used (1000 samples randomly extracted) to estimate the model parameters.

Predictors used in the multivariable models were detected through stepwise regression approach that combines forward and backward selection methods in an iterative procedure (significance level of 0·05 both for entry and retention). Potential independent predictors were: patient characteristics at baseline (age, sex, body mass index (BMI), geo-economic area), chronic disease (chronic obstructive pulmonary disease (COPD), diabetes mellitus, immune-incompetence, cardiac failure, renal failure, liver failure), presence of ARDS risk factors, ICU's

characteristics (number of beds, proportion of ICU beds in hospital, number of beds per physician and per nurse, academic ICU), clinical parameters measured at second day from ARDS onset (total respiratory rate, tidal volume, presence of controlled ventilation, PEEP, standardized minute ventilation, ARDS severity, dynamic compliance, partial pressure of carbon dioxide ($PaCO_2$), pH, non-pulmonary sequential organ failure assessment (SOFA) score, presence of adjunctive measures performed during two day from ARDS onset). Moreover, when sex was identified as a statistical significant predictor, we also evaluated its interaction with other selected predictors.

All p-values were two-sided, with p-values <0·05 considered as statistically significant.

Statistical analyses were performed with R, version 3.5.2. (R Project for Statistical Computing, http://www.R-project.org) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Supplemental Tables

Table e1. Ventilatory management and illness severity of female and male patients on second day of ARDS.

	Female	Male	p-value [0]
Patients in ICU at 2nd day, n (%)	871 (96.24)	1,427 (96.94)	0.3553
Invasive ventilation settings (2nd day)			
Patients undergoing controlled ventilation, n (%)	478 (59.4)	535 (40.9)	0.8872
Patients undergoing spontaneous ventilation, n (%)			
All patients	327 (40.6)	535 (40.9)	0.8872
Resolved ARDS	71 (47.3)	115 (44.2)	0.5433
Mild	97 (46.2)	147 (46.0)	0.9286
Moderate	115 (38.9)	194 (37.4)	0.6771
Severe	26 (27.7)	46 (32.2)	0.4604
Set respiratory rate (breaths/min), mean ± SD	18.5 ± 7.0	18.8 ± 6.6	0.1782
Total respiratory rate (breaths/min), mean ± SD	21.0 ± 6.3	20.8 ± 6.1	0.9149
Tidal volume (ml/kg IBW), mean ± SD			
All patients	8.1 ± 2.3	7.4 ± 1.7	<.0001
Patients with control ventilation	7.9 ± 2.0	7.1 ± 1.4	<.0001
Patients with spontaneous ventilation	8.5 ± 2.7	7.8 ± 2.0	<.0001
P-value (control vs spontaneous ventilation)	0.0008	<.0001	-
Lower tidal volume[1], n (%)	388 (51.1)	875 (70.5)	<.0001
Set PEEP (cmH_2O), mean ± SD	8.6 ± 3.6	8.5 ± 3.4	0.9978
Peak pressure [2] (cmH_2O), mean ± SD	27.0 ± 8.4	25.7 ± 7.9	0.0004
Dynamic compliance (ml/cmH_2O), mean ± SD	27.79 ± 17.69	34.41 ± 26.82	<.0001
Patients in whom P_{PLAT} measured, n (%)	300 (34.4)	511 (35.8)	0.5061
P_{PLAT} (cmH_2O) [3] , mean ± SD	23.9 ± 5.8	22.4 ± 5.5	0.0005
Driving pressure (cmH_2O) [3] , mean ± SD	15.1 ± 5.5	13.5 ± 4.8	0.0001
Standardized minute ventilation (l/min) [4] , mean ± SD	9.39 ± 4.28	11.21 ± 4.49	<.0001
Standardized minute ventilation (l/min/Kg IBW) [4] , mean ± SD	0.18 ± 0.08	0.16 ± 0.07	<.0001
Gas exchange (2nd day)			
P_aO_2 / FiO_2 (mmHg), mean ± SD	195.6 ± 85.8	196 ± 86.2	0.9636
SpO_2 , median [IQR]	97.0 [94.0 ; 98.0]	97.0 [95.0 ; 98.0]	0.1328
P_aCO_2 (mmHg), mean ± SD	43.7 ± 14.5	44.0 ± 12.4	0.0549
<35	163 (20.8)	241 (18.4)	0.1873
35 ⊢ 45	354 (45.1)	584 (44.7)	0.8341
≥ 45	267 (34.1)	482 (36.9)	0.1926
pH , mean ± SD	7.37 ± 0.10	7.37 ± 0.10	0.1204
Severity profile (2nd day)			
ARDS severity [5], n (%)			0.5114
Resolved ARDS, n (%)	179 (22.7)	324 (24.4)	
Mild, n (%)	215 (27.3)	331 (25.0)	
Moderate, n (%)	300 (38.1)	525 (39.6)	
Severe, n (%)	94 (11.9)	146 (11.0)	
SOFA score [6], mean ± SD	9.5 ± 4.6	9.7 ± 4.5	0.1439
Non pulmonary SOFA score [6], mean ± SD	6.8 ± 4.3	7.0 ± 4.2	0.3144
FiO_2, median [IQR]	0.5 [0.4 ; 0.6]	0.5 [0.4 ; 0.6]	0.9865

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; FiO_2: Fraction of Inspired oxygen; IBW: Ideal Body Weight; IQR: interquartile range (1^{st} quartile and 3^{rd} quartile); P_aCO_2 partial pressure of carbon dioxide; P_aO_2: arterial oxygen partial pressure; PEEP: Positive End-Expiratory Pressure; P_{PLAT}: Plateau Pressure; SD: Standard Deviation; SOFA: Sequential Organ Failure Assessment; SpO_2: peripheral oxygen saturation.

0. Comparison of male versus female patients.

1. Low tidal volume was defined as tidal volume ≤ 8 ml/IBW kg.

2. For peak pressure measurements patients receiving high frequency oscillatory ventilation (HFOV) or extracorporeal membrane oxygenation (ECMO) were excluded.

3. P_{PLAT} and driving pressure values are limited to patients in whom this value was reported, and in whom either an assist control mode was used or, where a mode permitting spontaneous ventilation was used, the set and total respiratory rates were equal. Patients receiving HFOV or ECMO were also excluded.

4. Standardized minute ventilation was calculated as minute ventilation × P_aCO_2 / 40.

5. At day 2, ARDS severity profile was evaluable for 788 females (90.5% on females in ICU at day 2) and for 1,326 males (92.9% on males in ICU at day 2).

6. For all SOFA scores, where data points were missing, this value was omitted and the denominator adjusted accordingly.

Table e2. Impact of sex on outcomes stratified by ARDS severity on second day of ARDS (n=2,377).

	Female (n = 905)	Male (n = 1,472)	p-value [1]
ICU mortality, n (%)			
All patients	320 (35.4)	518 (35.2)	0.9333
Resolved ARDS	40 (22.3)	92 (28.4)	0.1399
Mild ARDS	57 (26.5)	100 (30.2)	0.3507
Moderate ARDS	103 (34.3)	183 (34.9)	0.8791
Severe ARDS	60 (63.8)	67 (45.9)	0.0066
Hospital mortality [2], n (%)			
All patients	362 (40.2)	590 (40.2)	0.9844
Resolved ARDS	50 (28.1)	105 (32.7)	0.2853
Mild ARDS	70 (33.0)	123 (37.2)	0.3128
Moderate ARDS	116 (38.7)	206 (39.2)	0.8714
Severe ARDS	64 (68.1)	73 (50.3)	0.0068
Invasive ventilator-free days (days) [3] in ICU, median [IQR]			
All patients	13.0 [0.0 ; 23]	10.5 [0.0 ; 22.0]	0.1616
Resolved ARDS	21.0 [0.0 ; 25.0]	17.0 [0.0 ; 25.0]	0.2537
Mild ARDS	19.0 [0.0 ; 24.0]	17.0 [0.0 ; 24.0]	0.6306
Moderate ARDS	10.5 [0.0 ; 22.0]	8.5 [0.0 ; 20.0]	0.1383
Severe ARDS	0.0 [0.0 ; 0.0]	0.0 [0.0 ; 15.0]	0.0697
Survivors at ICU discharge	22.0 [16.0 ; 25.0]	20.0 [13.0 ; 25.0]	0.0134
Resolved ARDS	24.0 [19.0 ; 26.0]	24.0 [16.5 ; 26.0]	0.9149
Mild ARDS	22.0 [16.5 ; 25.0]	22.0 [16.0 ; 25.0]	0.7616
Moderate ARDS	20.0 [12.0 ; 23.0]	18.0 [10.0 ; 23.0]	0.0406
Severe ARDS	19.0 [10.0 ; 23.0]	15.0 [0.0 ; 20.0]	0.0624
Duration of invasive mechanical ventilation (days) [4] in ICU, median [IQR]			
All patients	7.0 [4.0 ; 13.0]	9.0 [4.0 ; 16.0]	0.0044
Resolved ARDS	6.0 [4.0 ; 12.0]	7.0 [3.0 ; 13.5]	0.5995
Mild ARDS	8.0 [4.0 ; 14.0]	8.0 [4.0 ; 15.0]	0.7828
Moderate ARDS	9.0 [5.0 ; 17.0]	11.0 [6.0 ; 19.0]	0.0231
Severe ARDS	8.0 [3.0 ; 16.0]	11.0 [5.0 ; 21.0]	0.0074
Survivors at ICU discharge	7.0 [4.0 ; 13.0]	9.0 [4.0 ; 16.0]	0.0124
Resolved ARDS	5.0 [3.0 ; 10.0]	5.0 [3.0 ; 12.5]	0.9094
Mild ARDS	7.0 [4.0 ; 12.5]	7.0 [4.0 ; 13.0]	0.7563
Moderate ARDS	9.0 [6.0 ; 17.0]	11.0 [6.0 ; 19.0]	0.0358
Severe ARDS	10.0 [6.0 ; 19.0]	14.0 [9.0 ; 31.0]	0.0587
Length of stay in ICU (days) [5], median [IQR]			
All patients	9.0 [5.0 ; 17.0]	11.0 [6.0 ; 20.0]	0.0014
Resolved ARDS	8.0 [5.0 ; 15.0]	9.5 [5.0 ; 19.0]	0.6258
Mild ARDS	11.0 [7.0 ; 17.0]	11.0 [6.0 ; 18.0]	0.6009
Moderate ARDS	12.0 [7.0 ; 21.0]	14.0 [8.0 ; 23.0]	0.0264
Severe ARDS	8.5 [4.0 ; 18.0]	13.5 [5.0 ; 25.0]	0.0056
Survivors at ICU discharge	11.0 [6.0 ; 18.0]	12.0 [7.0 ; 22.0]	0.0094
Resolved ARDS	8.0 [5.0 ; 14.0]	9.0 [5.0 ;19.5]	0.5724
Mild ARDS	11.0 [7.0 ; 16.0]	11.0 [6.0 ; 18.0]	0.6144

Moderate ARDS	13.0 [8.0 ; 23.0]	15.0 [9.0 ; 25.0]	0.0682
Severe ARDS	12.0 [7.0 ; 21.0]	17.0 [10.0 ; 31.0]	0.0669
Length of stay in hospital (days) [6] , median [IQR]			
All patients	16.0 [8.0 ; 29.0]	18.0 [9.0 ; 35.0]	0.0006
Resolved ARDS	16.0 [9.0 ; 31.0]	16.0 [9.0 ; 32.0]	0.9428
Mild ARDS	19.0 [11.0 ; 35.5]	19.0 [11.0 ; 35.0]	0.5340
Moderate ARDS	17.0 [9.0 ; 30.0]	20.5 [10.5 ; 40.0]	0.0029
Severe ARDS	10.0 [4.0 ; 21.0]	18.0 [6.0 ; 39.0]	0.0003
Survivors at hospital discharge	21.0 [13.0 ; 36.0]	25.0 [14.0 ; 44.0]	0.0012
Resolved ARDS	19.0 [12.0 ; 33.5]	23.0 [11.0 ; 40.0]	0.2820
Mild ARDS	24.0 [14.0 ; 40.0]	22.5 [14.0 ; 41.0]	0.8964
Moderate ARDS	23.0 [14.0 ; 37.0]	27.0 [16.0 ; 52.0]	0.0033
Severe ARDS	20.5 [10.0 ; 31.5]	32.0 [16.0 ; 51.0]	0.0124
Limitation of life sustaining measures in ICU, n (%)			
All patients	225 (24.9)	353 (24.0)	0.6269
Resolved ARDS	41 (22.9)	68 (21.0)	0.6173
Mild ARDS	48 (22.3)	73 (22.1)	0.9406
Moderate ARDS	67 (22.3)	130 (24.8)	0.4312
Severe ARDS	36 (38.3)	43 (29.5)	0.1546
Deaths in ICU after limitation, n (%) [7]	179 (79.6)	285 (80.7)	0.7279
All patients (with limitation)			
Resolved ARDS	27 (65.9)	55 (80.9)	0.0783
Mild ARDS	37 (77.1)	53 (72.6)	0.5807
Moderate ARDS	53 (79.1)	111 (85.4)	0.2635
Severe ARDS	32 (88.9)	32 (74.4)	0.1024
Time to limitation in ICU, mean ± SE [8]			
All patients (with limitation)	50.5 ± 3.1	54.7 ± 1.9	0.0834
Resolved ARDS	44.8 ± 3.4	58.7 ± 4.2	0.4607
Mild ARDS	48.6 ± 6.0	55.3 ± 4.2	0.8187
Moderate ARDS	58.1 ± 4.2	56.0 ± 3.0	0.5169
Severe ARDS	47.9 ± 5.9	49.2 ± 5.2	0.0321

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit; IQR: interquartile range (1st quartile; 3rd quartile). SE: standard error.

1. Comparison of male versus female patients.

2. Vital status at hospital discharge was not evaluable for 9 patients (4 females and 5 males).

3. Invasive ventilator-free days were calculated as the number of days from weaning from invasive mechanical ventilation to the date of ICU discharge. Patients who died before weaning were considered to have a ventilator-free-day value of 0.

4. Duration of invasive mechanical ventilation was assessed during ICU stay and it was calculated as the number of days between the date of intubation and the date of extubation performed in ICU.

5. Length of stay in ICU was calculated as the number of days between the date of ICU admission and the date of ICU discharge (or 90 when discharge occurred after 90 days).

6. Length of stay in hospital was calculated as the number of days between the date of ICU admission and the date of hospital discharge (or 90 when discharge occurred after 90 days).

7. Percentage is calculated on patients with limitation of life sustaining measures.

8. Mean time to limitation of life sustaining measures in ICU was estimated with Kaplan-Meier approach, considering as censored those patients discharged from ICU.

Table e3. Tests of Fixed Effects in linear model for repeated measures of tidal volume.

Effect	F value	p-value
Sex	95.80	<.0001
Day of follow-up	1.92	0.0537
Interaction term *[Sex × Day of follow-up]*	1.59	0.1215

Table e4. Factors associated with the use of lower tidal volume (tidal volume of ≤ 8ml/kg IBW) at the first day of ARDS.

Parameter	OR (95% CI)
Total respiratory rate (breaths/min)	1.106 (1.085-1.130)
$PaCO_2$ (mmHg)	1.028 (1.019-1.038)
Controlled ventilation (ref. Spontaneous)	2.023 (1.564-2.616)
Geoeconomic area (ref. Europe high income)	
Rest of World high income	1.464 (1.027-2.086)
Middle income	1.440 (0.991-2.090)
pH (0.1 unit)	1.014 (1.003-1.024)
Chronic liver failure (ref. No)	1.877 (1.013-3.479)
No adjunctive measures during 1^{st} or 2^{nd} day (ref. Yes)	1.317 (1.009-1.719)
Male (ref. Female)	
Height < 1.70 m	2.602 (1.297-5.220)
Height ≥ 1.70 m	0.772 (0.414-1.442)
Random effects, estimate (95% CI)	
Intercept for ICU cluster, SD	*0.840 (0.667 ; 1.059)*

Table e5. Generalized linear mixed models on patients in ICU at the second day (n=2,298).

Outcome – Length of stay in ICU in survivors at ICU discharge (n=1,523)	**IRR (95% CI)**
Fixed effects	
Sex (ref. Female)	1.260 (1.213 ; 1.309)
Age (years)	1.002 (1.001 ; 1.003)
Adjunctive measures during 1st or 2nd day (ref. Yes)	0.812 (0.777 ; 0.848)
Adjusted non-pulmonary SOFA score at 2nd day	1.021 (1.016 ; 1.026)
Dynamic compliance at 2nd day (ml/cmH_2O)	0.994 (0.993 ; 0.995)
PEEP at 2nd day (cmH_20)	1.016 (1.010 ; 1.022)
ARDS severity at 2nd day (ref. Resolved ARDS)	
Mild ARDS at 2nd day	0.961 (0.912 ; 1.013)
Moderate ARDS at 2nd day	1.093 (1.040 ; 1.148)
Severe ARDS at 2nd day	1.260 (1.169 ; 1.358)
Random effects, estimate (95% CI)	
Intercept for ICU cluster, SD	*0.573 (0.524 ; 0.625)*
Outcome – Length of stay in hospital in survivors patients at hospital discharge (n=1,400)	**IRR (95% CI)**
Fixed effects	
Sex (ref. Female)	1.181 (1.147 ; 1.216)
Age (year)	1.002 (1.002 ; 1.003)
Chronic cardiac failure (ref. No)	0.747 (0.707 ; 0.789)
Adjusted non-pulmonary SOFA score at 2nd day	1.028 (1.024 ; 1.031)
Dynamic compliance at 2nd day (ml/cmH_2O)	0.998 (0.997 ; 0.998)
PEEP at 2nd day (cmH_20)	1.012 (1.008 ; 1.017)
Geo-economic area (ref. Rest of World high income)	
Europe high income	1.335 (1.133 ; 1.574)
Middle income	1.184 (0.983 ; 1.425)
Random effects, estimate (95% CI)	
Intercept for ICU cluster, SD	*0.547 (0.502 ; 0.596)*
Outcome – Duration of mechanical ventilation in ICU in surviving patients at ICU discharge (n=1,523)	**IRR (95% CI)**
Fixed effects	
Sex (ref. Female)	1.247 (1.190 ; 1.307)
COPD (ref. No)	0.845 (0.799 ; 0.894)
Chronic liver failure (ref. No)	0.687 (0.589 ; 0.801)
Adjunctive measures during 1st or 2nd day (ref. Yes)	0.858 (0.814 ; 0.905)
Mode control of ventilation at 2nd day (ref. No)	1.176 (1.113 ; 1.242)
Adjusted non-pulmonary SOFA score at 2nd day	1.030 (1.024 ; 1.037)
Dynamic compliance at 2nd day (ml/cmH_2O)	0.994 (0.993 ; 0.995)
PEEP at 2nd day (cmH_20)	1.017 (1.010 ; 1.024)
ARDS severity at 2nd day (ref. Resolved ARDS)	
Mild ARDS at 2nd day	0.948 (0.889 ; 1.012)
Moderate ARDS at 2nd day	1.073 (1.010 ; 1.140)
Severe ARDS at 2nd day	1.490 (1.361 ; 1.631)
Random effects, estimate (95% CI)	
Intercept for ICU cluster, SD	*0.635 (0.580 ; 0.696)*

Outcome – Hospital mortality (90 days) (n=2,298)	OR (95% CI)
Fixed effects	
Age (year)	1.026 (1.018 ; 1.033)
BMI (kg/m^2)	0.974 (0.957 ; 0.991)
Immuno-incompetence (ref. No)	1.933 (1.436 ; 2.601)
Chronic liver failure (ref. No)	2.441 (1.330 ; 4.479)
pH at 2nd day (0.1 unit)	0.976 (0.964 ; 0.989)
Adjusted non-pulmonary SOFA score at 2nd day	1.151 (1.114 ; 1.189)
Total respiratory rate at 2nd day (breaths/min)	1.047 (1.026 ; 1.069)
Geo-economic area (ref. Middle income)	
Europe high income	0.662 (0.463 ; 0.946)
Rest of World high income	0.432 (0.282 ; 0.663)
Resolved ARDS at 2nd day	
Sex (ref. Female)	0.957 (0.548 ; 1.672)
Mild ARDS at 2nd day	
Sex (ref. Female)	1.326 (0.643 ; 2.734)
Moderate ARDS at 2nd day	
Sex (ref. Female)	1.075 (0.550 ; 2.103)
Severe ARDS at 2nd day	
Sex (ref. Female)	0.347 (0.144 ; 0.833)
Random effects, estimate (95% CI)	
Intercept for ICU cluster, SD	*0.624 (0.432 ; 0.903)*
Outcome – ICU mortality (90 days) (n=2,298)	**OR (95% CI)**
Fixed effects	
Age (year)	1.019 (1.011 ; 1.027)
BMI (kg/m^2)	0.979 (0.962 ; 0.997)
Immuno-incompetence (ref. No)	1.791 (1.325 ; 2.422)
Chronic liver failure (ref. No)	2.228 (1.224 ; 4.057)
pH at 2nd day (0.1 unit)	0.974 (0.962 ; 0.987)
Adjusted non-pulmonary SOFA score at 2nd day	1.157 (1.119 ; 1.196)
Total respiratory rate at 2nd day (breaths/min)	1.059 (1.037 ; 1.081)
Geo-economic area (ref. Middle income)	
Europe high income	0.600 (0.416 ; 0.866)
Rest of World high income	0.383 (0.246 ; 0.596)
Resolved ARDS at 2nd day	
Sex (ref. Female)	1.183 (0.660 ; 2.119)
Mild ARDS at 2nd day	
Sex (ref. Female)	0.914 (0.429 ; 1.949)
Moderate ARDS at 2nd day	
Sex (ref. Female)	0.823 (0.410 ; 1.652)
Severe ARDS at 2nd day	
Sex (ref. Female)	0.294 (0.121 ; 0.716)
Random effects, estimate (95% CI)	
Intercept for ICU cluster, SD	*0.670 (0.478 ; 0.939)*

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; BMI: body mass index; CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; IBW: Ideal Body Weight; ICU: intensive care unit; IRR: incidence rate ratio; OR: odds ratio; PEEP: Positive End-Expiratory Pressure; SD: standard deviation; SOFA: Sequential Organ Failure Assessment.

Table e6. Demographics, ventilatory management and illness severity of female and male patients with severe 'confirmed' ARDS.

	Female	Male	p-value [1]
Patients in ICU at 2nd day with severe ARDS, n	94	146	-
Age (years), mean ± SD	59.0 ± 18.1	59.2 ± 17.3	0.9878
Height (m), mean ± SD	1.60 ± 0.08	1.72 ± 0.08	<.0001
BMI (kg/m^2), mean ± SD	29.4 ± 10.8	27.2 ± 7.2	0.6127
Chronic disease, n (%):			
COPD	20 (21.3)	36 (24.7)	0.5455
Diabetes mellitus	24 (25.5)	33 (22.6)	0.6027
Immuno-incompetence (all types)	24 (25.5)	25 (17.2)	0.1147
Chronic cardiac failure	10 (10.6)	14 (9.6)	0.7914
Chronic renal failure	5 (5.3)	11 (7.5)	0.5019
Chronic liver failure	2 (2.13)	2 (1.37)	0.6457
Risk factor for ARDS [2], n (%):			
Pneumonia	67 (71.3)	97 (66.4)	0.4316
Non-pulmonary sepsis	14 (14.9)	20 (13.7)	0.7955
Aspiration of gastric contents	15 (16.0)	18 (12.3)	0.4256
Non-cardiogenic shock	8 (8.5)	19 (13.0)	0.2812
Major trauma	0 (0.0)	7 (4.8)	0.0446
Blood transfusion	6 (6.4)	9 (6.2)	0.9456
Pulmonary contusion	1 (1.1)	7 (4.8)	0.1534
Inhalation injury	1 (1.1)	7 (4.8)	0.1534
Drug overdose	2 (2.13)	0 (0.00)	0.1524
Pulmonary vasculitis	1 (1.1)	0 (0.0)	0.3917
Severe burns	1 (1.1)	1 (0.7)	1.0000
Drowning	0 (0.00)	0 (0.00)	-
Pancreatitis	0 (0.00)	5 (3.42)	0.1597
Other	2 (2.1)	1 (0.7)	0.5627
Risk factor for ARDS, n (%):			0.8636
Only pulmonary risk factors	13 (13.8)	26 (17.8)	
Only non-pulmonary risk factors	62 (66.0)	91 (62.3)	
Both	15 (16.0)	22 (15.1)	
No risk factor	4 (4.3)	7 (4.8)	
Type of admission, n (%)			0.6273
Medical	79 (84.0)	114 (78.1)	
Postoperative (elective)	2 (2.1)	3 (2.1)	
Surgical	11 (11.7)	22 (15.1)	
Trauma	2 (2.1)	7 (4.8)	
Clinician recognition of ARDS, n (%)			
At baseline	51 (54.3)	87 (59.6)	0.4146
During ICU stay	82 (87.2)	130 (89.0)	0.6704
Invasive ventilation settings (2nd day)			
Patients undergoing controlled ventilation, n (%)	68 (72.3)	97 (67.8)	0.4604
Set respiratory rate (breaths/min), mean ± SD	22.7 ± 7.7	19.3 ± 7.2	0.0008
Total respiratory rate (breaths/min), mean ± SD	24.2 ± 7.2	22.1 ± 6.0	0.0182

Tidal volume (ml/kg IBW), mean ± SD			
All patients	7.4 ± 2.4	7.2 ± 1.8	0.2336
Patients with control ventilation	7.7 ± 2.0	7.1 ± 1.5	0.0181
Patients with spontaneous ventilation	6.7 ± 3.3	7.6 ± 2.3	0.2074
P-value (control vs spontaneous ventilation)	0.1262	0.1145	-
Lower tidal volume [3], n (%)	57 (62.6)	102 (74.5)	0.0572
Set PEEP (cmH_2O), mean ± SD	10.4 ± 3.8	10.5 ± 3.1	0.6585
Peak pressure [4] (cmH_2O), mean ± SD	31.9 ± 8.6	29.7 ± 7.9	0.0268
Dynamic compliance (ml/cmH_2O), mean ± SD	20.82 ± 11.65	31.69 ± 26.72	<.0001
Patients in whom P_{PLAT} measured, n (%)	44 (46.8)	62 (42.5)	0.5084
P_{PLAT} (cmH_2O) [5] , mean ± SD	27.7 ± 5.6	25.5 ± 5.3	0.0787
Driving pressure (cmH_2O) [5] , mean ± SD	17.5 ± 5.6	14.7 ± 4.9	0.0195
Standardized minute ventilation (l/min) [6] , mean ± SD	11.68 ± 5.91	13.24 ± 5.93	0.0355
Standardized minute ventilation (l/min/Kg IBW) [6] , mean ± SD	0.23 ± 0.11	0.20 ± 0.09	0.0125
Gas exchange (2nd day)			
P_aO_2 / FiO_2 (mmHg), mean ± SD	77.1 ± 16.3	77.9 ± 15.1	0.8917
SpO_2 , median [IQR]	94.0 [89.0 ; 96.0]	93.0 [90.0 ; 95.0]	0.4423
P_aCO_2 (mmHg), mean ± SD	53.2 ± 24.4	50.2 ± 17.2	0.9870
<35	15 (16.0)	19 (13.1)	0.5372
35 ⊢ 45	26 (27.7)	50 (34.5)	0.2685
≥ 45	53 (56.4)	76 (52.4)	0.5476
pH , mean ± SD	7.31 ± 0.14	7.31 ± 0.12	0.6771
Severity profile (2nd day)			
SOFA score [7], mean ± SD	12.7 ± 4.4	12.5 ± 4.5	0.7545
Non pulmonary SOFA score [7], mean ± SD	8.2 ± 4.3	7.8 ± 4.1	0.5798
FiO_2, median [IQR]	0.9 [0.8 ; 1.0]	0.9 [0.8 ; 1.0]	0.8330
Adjunctive measures (first 48 hours)			
Neuromuscular blockade	37 (39.4)	45 (30.8)	0.1733
Recruitment maneuvers	31 (33.0)	41 (28.1)	0.4191
Prone positioning	17 (18.1)	15 (10.3)	0.0823
ECMO	12 (12.8)	5 (3.4)	0.0059
Inhaled vasodilators	18 (19.1)	8 (5.5)	0.0009
HFOV	0 (0.0)	1 (0.7)	1.0000
None of the above	25 (26.6)	68 (46.6)	0.0019

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; ECMO: Extracorporeal Membrane Oxygenation; FiO_2: Fraction of Inspired oxygen; HFOV: High Frequency Oscillatory Ventilation; IBW: Ideal Body Weight; ICU: Intensive Care Unit; IQR: interquartile range (1st quartile and 3rd quartile); P_aCO_2 partial pressure of carbon dioxide; P_aO_2: arterial oxygen partial pressure; PEEP: Positive End-Expiratory Pressure; P_{PLAT}: Plateau Pressure; SD: Standard Deviation; SOFA: Sequential Organ Failure Assessment; SpO_2: peripheral oxygen saturation.

1. Comparison of male versus female patients.

2. Total is greater than 100%, since patients could have more than one risk factor.

3. Low tidal volume was defined as tidal volume ≤ 8 ml/IBW kg.

4. For peak pressure measurements patients receiving HFOV or ECMO were excluded.

5. P_{PLAT} and driving pressure values are limited to patients in whom this value was reported, and in whom either an assist control mode was used or, where a mode permitting spontaneous ventilation was used, the set and total respiratory rates were equal. Patients receiving HFOV or ECMO were also excluded.

6. Standardized minute ventilation was calculated as minute ventilation × P_aCO_2 / 40.

7. For all SOFA scores, where data points were missing, this value was omitted and the denominator adjusted accordingly.

Table e7. Impact of sex and geo-economic region on outcomes of ARDS.

	Geo-economic region			
	Europe high income (n = 1,263)	**Rest of world high income (n = 649)**	**Middle income (n = 465)**	**p-value [1]**
Number of patients, n (%)				
Female	465 (36.8)	253 (39.0)	187 (40.2)	0.3720
Male	798 (63.2)	396 (61.0)	278 (59.8)	
Invasive ventilator-free days (days) [2] in ICU, median [IQR]				
All patients	8.0 [0.0 ; 22.0]	18.0 [0.0 ; 24.0]*	5.0 [0.0 ; 22.0]†	<.0001
Female	6.0 [0.0 ; 22.0]	21.0 [0.0 ; 24.0]*	7.0 [0.0 ; 22.0]†	<.0001
Male	8.5 [0.0 ; 22.00]	17.0 [0.0 ; 24.0]*	1.0 [0.0 ; 20.0]†	<.0001
p-value (comparison between genders)	0.7833	0.1288	0.1787	-
Survivors at ICU discharge	20.0 [11.5 ; 25.0]	22.0 [17.0 ; 25.0]*	20.0 [15.0 ; 24.0]†	<.0001
Female	21.0 [14.0 ; 24.0]	23.0 [18.0 ; 25.0]*	22.0 [17.0 ; 25.0]	0.0199
Male	19.0 [10.0 ; 25.0]	22.0 [17.0 ; 26.0]*	20.0 [15.0 ; 24.0]†	<.0001
p-value (comparison between genders)	0.1193	0.9682	0.0121	-
Duration of invasive mechanical ventilation (days) [3] in ICU, median [IQR]				
All patients	8.0 [4.0 ; 16.0]	7.0 [4.0 ; 13.0]*	9.0 [4.0 ; 16.0]†	<.0001
Female	8.0 [4.0 ; 14.0]	6.0 [4.0 ; 12.0]	8.0 [4.0 ; 14.0]	0.3420
Male	9.0 [4.0 ; 18.0]	7.0 [3.0 ; 13.0]*	9.0 [5.0 ; 17.0]†	<.0001
p-value (comparison between genders)	0.0170	0.8949	0.0283	-
Survivors at ICU discharge	9.0 [4.0 ; 17.5]	7.0 [4.0 ; 12.0]*	9.0 [5.0 ; 14.0]†	<.0001
Female	8.0 [5.0 ; 15.0]	6.0 [4.0 ; 11.0]*	7.0 [4.0 ; 12.0]	0.0205
Male	10.0 [4.0 ; 19.0]	7.0 [3.0 ; 12.0]*	9.0 [5.0 ; 14.0]†	<.0001
p-value (comparison between genders)	0.1070	0.9812	0.0125	-
Length of stay in ICU (days) [4], median [IQR]				
All patients	11.0 [5.0 ; 21.0]	9.0 [5.0 ; 16.0]*	11.0 [6.0 ; 19.0]†	0.0042
Female	10.0 [5.0 ; 18.0]	9.0 [.0 ; 15.0]	9.0 [5.0 ; 18.0]	0.6536
Male	11.0 [6.0 ; 23.0]	10.0 [5.0 ; 17.0]*	12.0 [7.0 ; 20.0]†	0.0027
p-value (comparison between genders)	0.0125	0.5942	0.0174	-
Survivors at ICU discharge	12.0 [7.0 ; 23.0]	10.0 [6.0 ; 16.0]*	12.0 [7.0 ; 20.0]†	<.0001
Female	12.0 [7.0 ; 21.0]	9.0 [6.0 ; 15.0]*	10.5 [6.0 ; 17.0]	0.0076
Male	12.0 [7.0 ; 24.0]	11.0 [5.0 ; 18.0]*	13.0 [8.0 ; 21.0]†	0.0007
p-value (comparison between genders)	0.2272	0.4359	0.0155	-
Length of stay in hospital (days) [5], median [IQR]				
All patients	18.0 [8.0 ; 36.0]	17.0 [8.0 ; 30.0]	16.0 [8.0 ; 28.0]*	0.0372
Female	16.0 [7.0 ; 30.0]	17.0 [9.0 ; 31.0]	14.0 [7.0 ; 25.0]	0.1018
Male	20.0 [9.0 ; 40.0]	17.0 [8.0 ; 29.0]*	17.0 [9.0 ; 30.0]	0.0134
p-value (comparison between genders)	0.0003	0.6402	0.0360	-
Survivors at hospital discharge	26.0 [14.0 ; 46.0]	20.5 [12.0 ; 35.0]	21.0 [12.0 ; 36.0]*	<.0001
Female	25.0 [14.5 ; 40.5]	19.0 [12.0 ; 34.0]	18.0 [11.0 ; 31.0]*	0.0037
Male	27.0 [14.0 ; 50.0]	22.0 [12.0 ; 37.0]*	22.0 [14.0 ; 40.0]	0.0025
p-value (comparison between genders)	0.0448	0.4060	0.0212	-
Limitation of life sustaining measures in ICU, n (%)				
All patients	339 (26.8)	157 (24.2)	82 (17.6)*†	0.0004

Female	133 (28.6)	57 (22.5)	35 (18.7)*	0.0183
Male	206 (25.8)	100 (25.3)	47 (16.9)*†	0.0088
p-value (comparison between genders)	0.2809	0.4295	0.6155	-

Abbreviations: ICU: Intensive Care Unit.

1. Comparison among geo-economic area.

2. Invasive ventilator-free days were calculated as the number of days from weaning from invasive mechanical ventilation to the date of ICU discharge. Patients who died before weaning were considered to have a ventilator-free-day value of 0.

3. Duration of invasive mechanical ventilation was assessed during ICU stay and it was calculated as the number of days between the date of intubation and the date of extubation performed in ICU.

4. Length of stay in ICU was calculated as the number of days between the date of ICU admission and the date of ICU discharge (or 90 when discharge occurred after 90 days).

5. Length of stay in hospital was calculated as the number of days between the date of ICU admission and the date of hospital discharge (or 90 when discharge occurred after 90 days).

** Comparison with "Europe high income group", p-value <0.05 (Bonferroni's correction).*

† Comparison with "Rest of word high income", p-value <0.05 (Bonferroni's correction).

Supplemental Figures

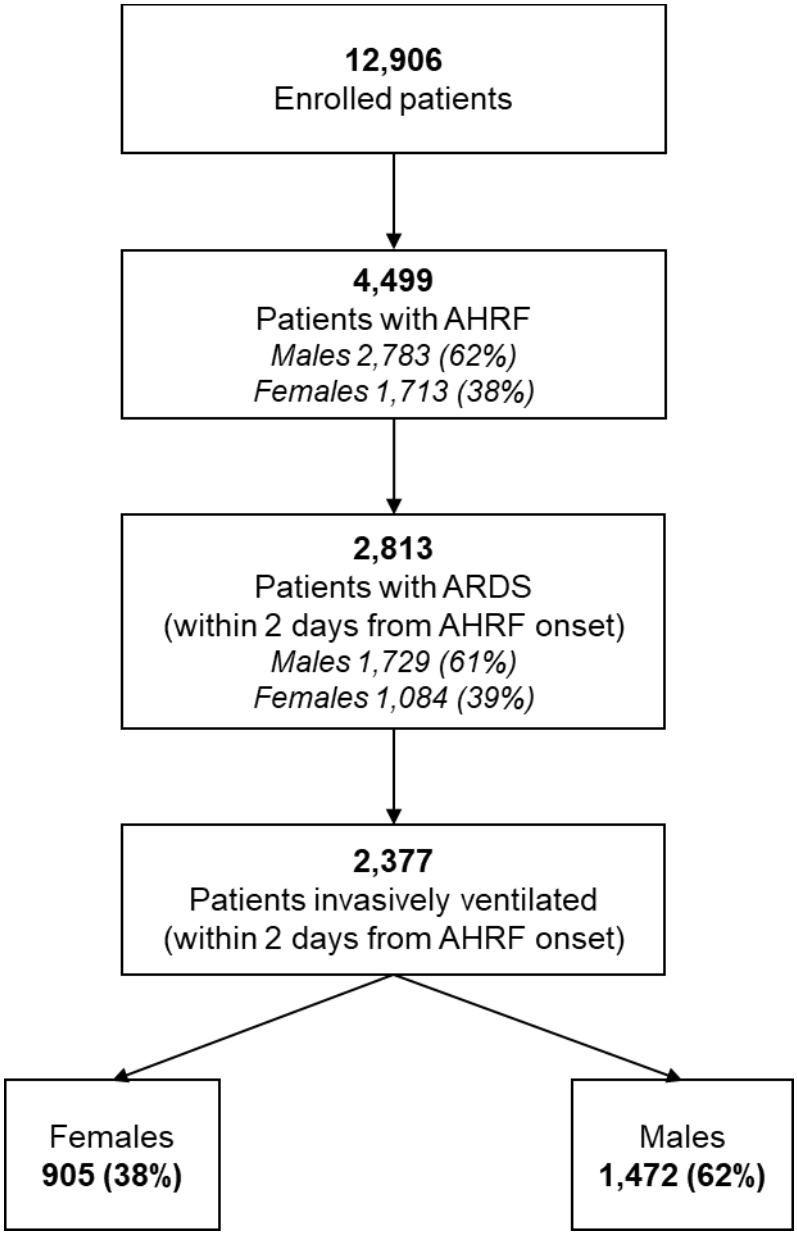


Figure e1. Flow-chart of study population.

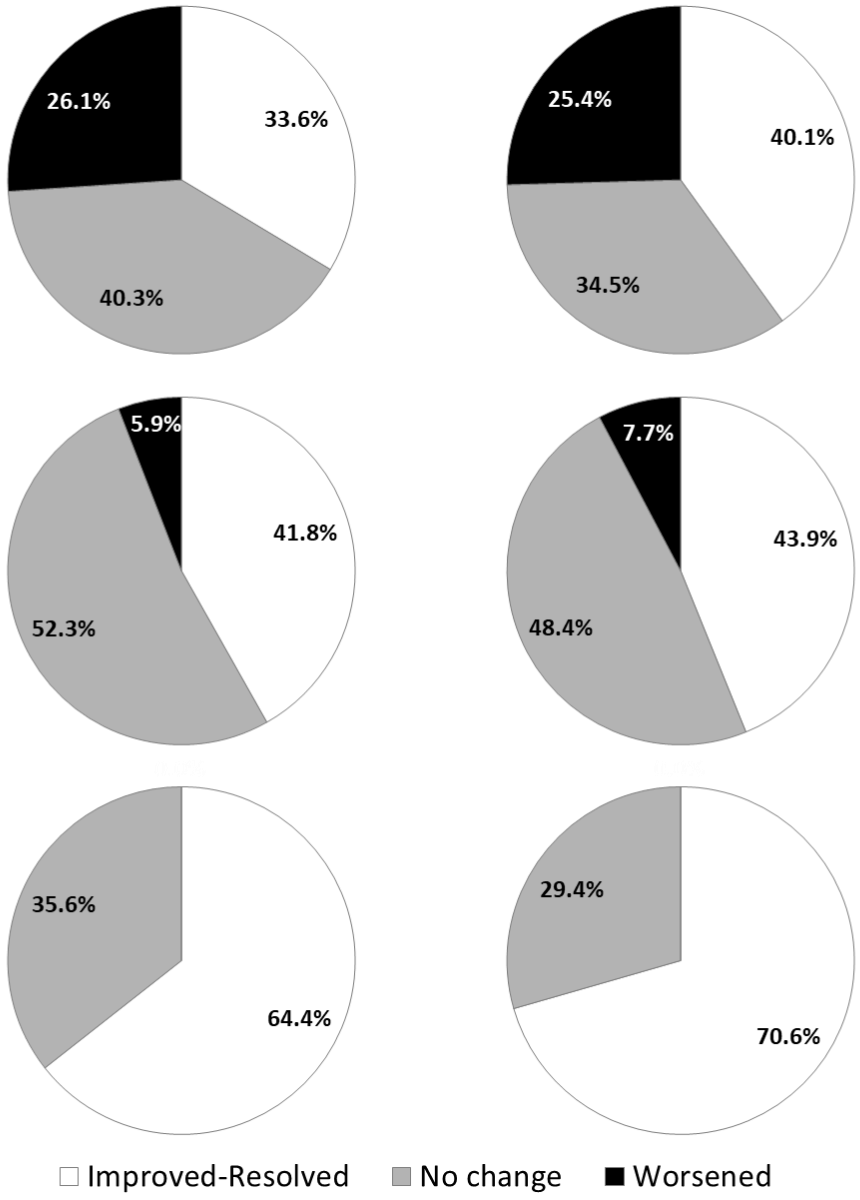


Figure e2. Progression of ARDS severity from first to second day in female and male patients with ARDS invasively ventilated.

Note: Progression of ARDS severity at second day was evaluable for 2,114 patients (92% on 2,298 alive patients in ICU at day 2). No statistically significance differences were observed between males and females in the progression of ARDS severity, whether in mild (p-value=0.2191), in moderate (p-value=0.3575) and in severe (p-value=0.1613) patients at day 1.

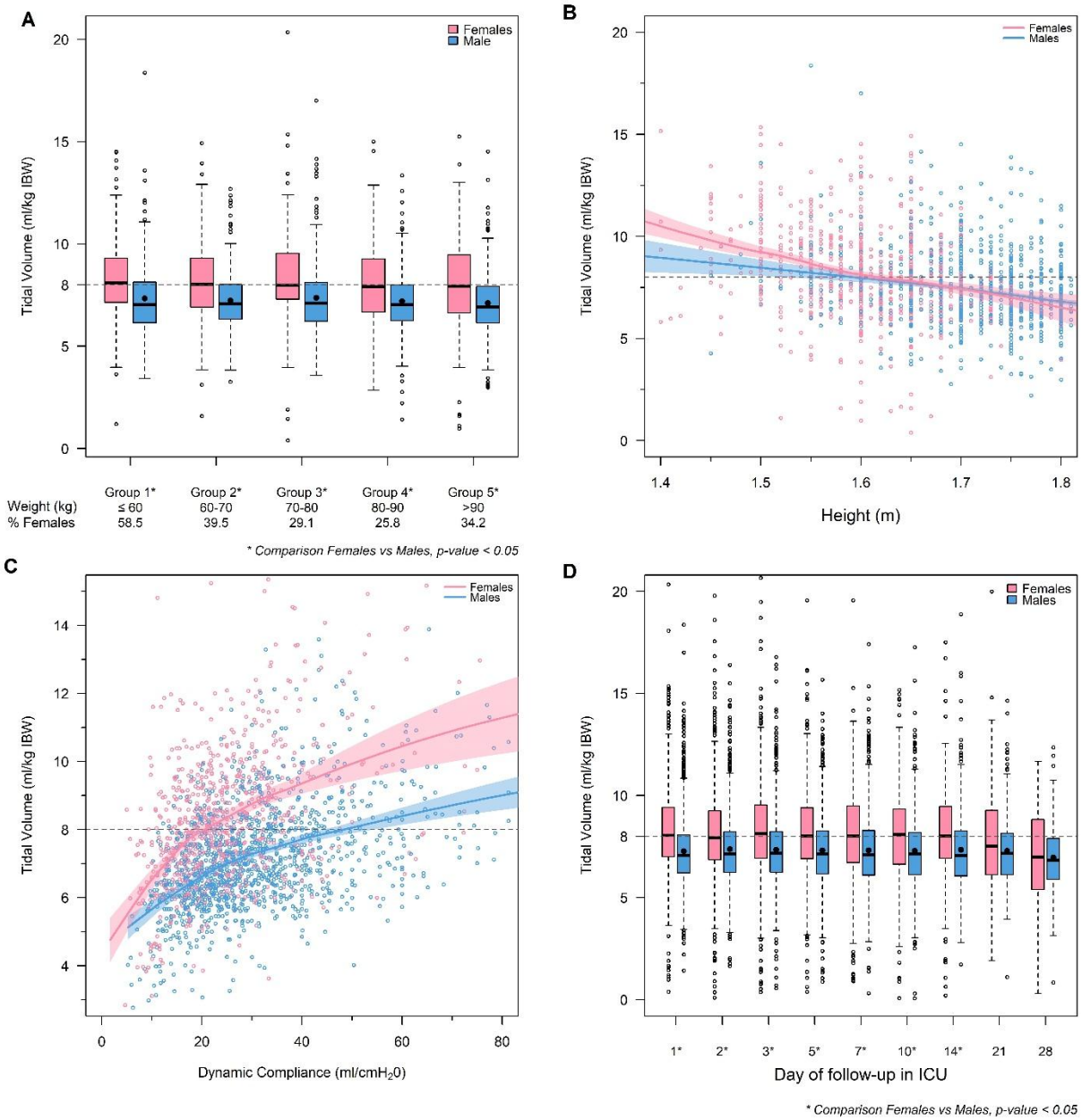


Figure e3. Use of tidal volumes in invasively ventilated female versus male patients with ARDS.

Panel A. Boxplot for tidal volume (ml/kg IBW) in male and female population stratified by quintiles of actual body weight in study population.
Note1: * refers to p-value < 0.05 for the comparison between females and males.
Note2: Pearson correlation coefficient between tidal volume and weight in females and males is 0.0011 (p=0.9751) and –0.0618 (p=0.0213), respectively.

Panel B. LOESS (locally estimated scatterplot smoothing) curve of relationship between tidal volume (ml/kg IBW) at first day of ARDS and height (meters) in males and females.
Note: LOESS curve uses a bandwidth 2/3 and 1 degree of polynomial regression.
Panel C. LOESS (locally estimated scatterplot smoothing) curve of relationship between tidal volume (ml/kg IBW) and dynamic compliance (ml/ cmH_2O) at first day of ARDS in males and females.
Note: LOESS curve uses a bandwidth 2/3 and 1 degree of polynomial regression.

Panel D. Changes in tidal volume (ml/kg IBW) during ICU stay in male and female patients with ARDS invasively ventilated.

Note: No trend during time was detected in both sexes. Trend was evaluated using linear model for repeated measures with unstructured covariance matrix [table e3].

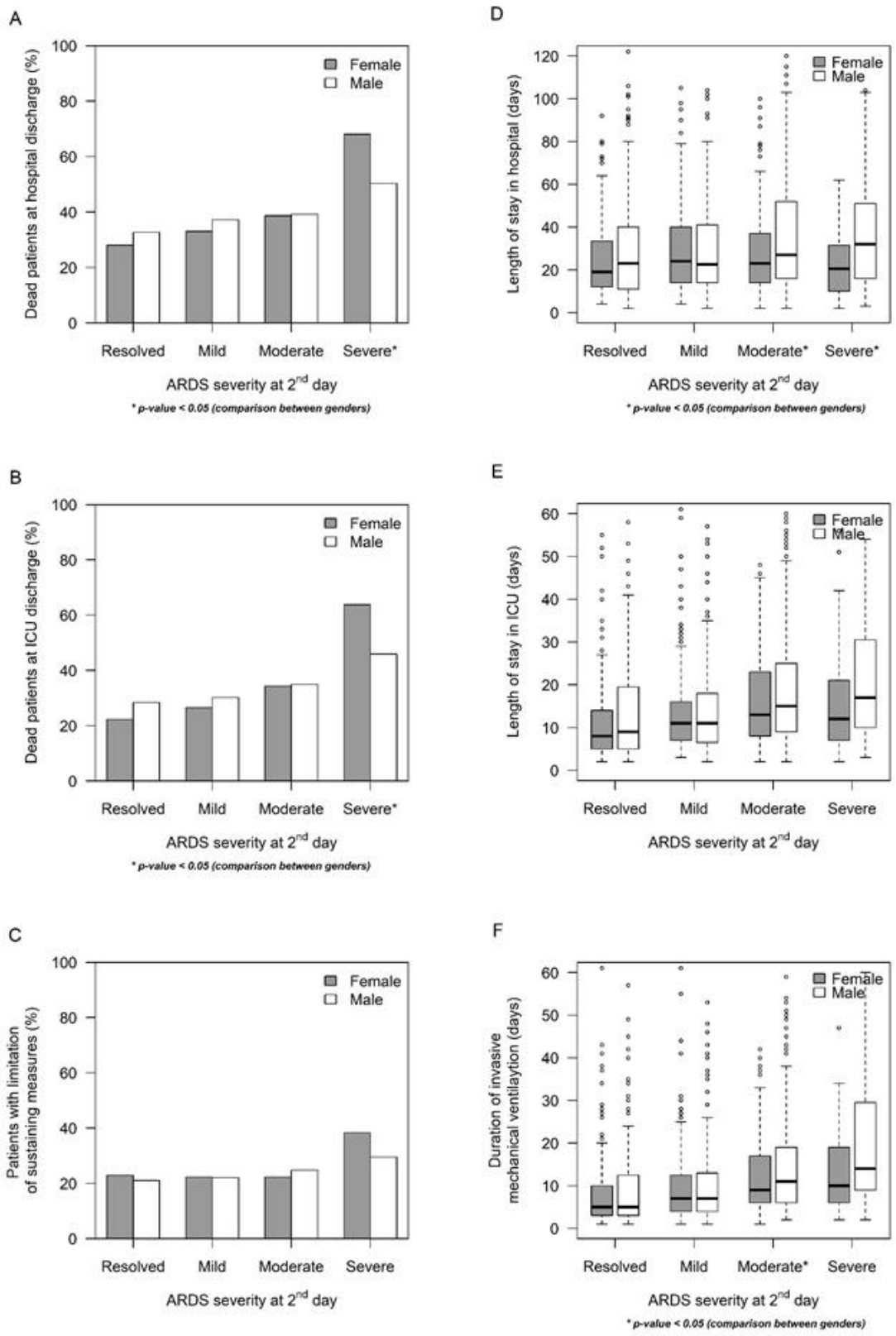


Figure e4. Outcomes in male and female patients stratified by ARDS severity at second day (resolved, mild, moderate and severe).

Panel A. Proportion of patients died at hospital discharge.

Panel B. Proportion of patients died at ICU discharge.

Panel C. Proportion of patients with limitation of sustaining measures in ICU.

Panel D. Boxplot for length of stay in hospital (days).

Panel E. Boxplot for length of stay in ICU (days).

Panel F. Boxplot for duration if invasive mechanical ventilation in ICU (days).

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Appendix 1: LUNG SAFE National coordinators, International Society/Network Endorsements, and Site Investigators

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National societies/Networks endorsing the study:

ANZICS Clinical Trials Group, Réseau Européen de Recherche en Ventilation Artificielle (ReVA Network); Irish Critical Care Trials Group; Société de Réanimation de Langue Française (SRLF); Société Française d'Anesthésie et de Réanimation (SFAR); Società Italiana Anestesia, Analgesia, Rianimazione e Terapia Intensiva (SIAARTI); The Japanese Society of Intensive Care Medicine (JSICM); Nonprofit Organization Japanese Society of Education for Physicians and Trainees in Intensive Care (JSEPTIC); UK Intensive Care Society.

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