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

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ONLINE DATA SUPPLEMENT

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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 (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.

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 1st or 2nd 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

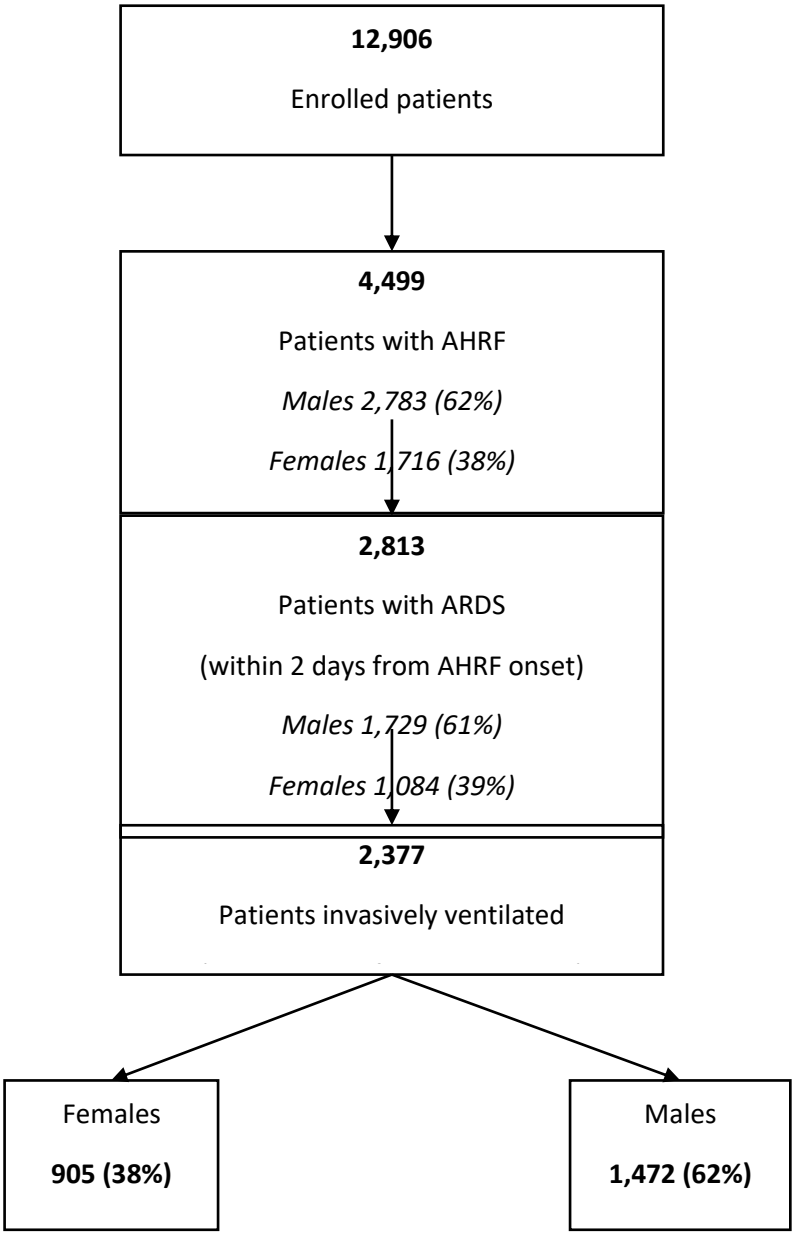

Figure e1. Flow-chart of study population.

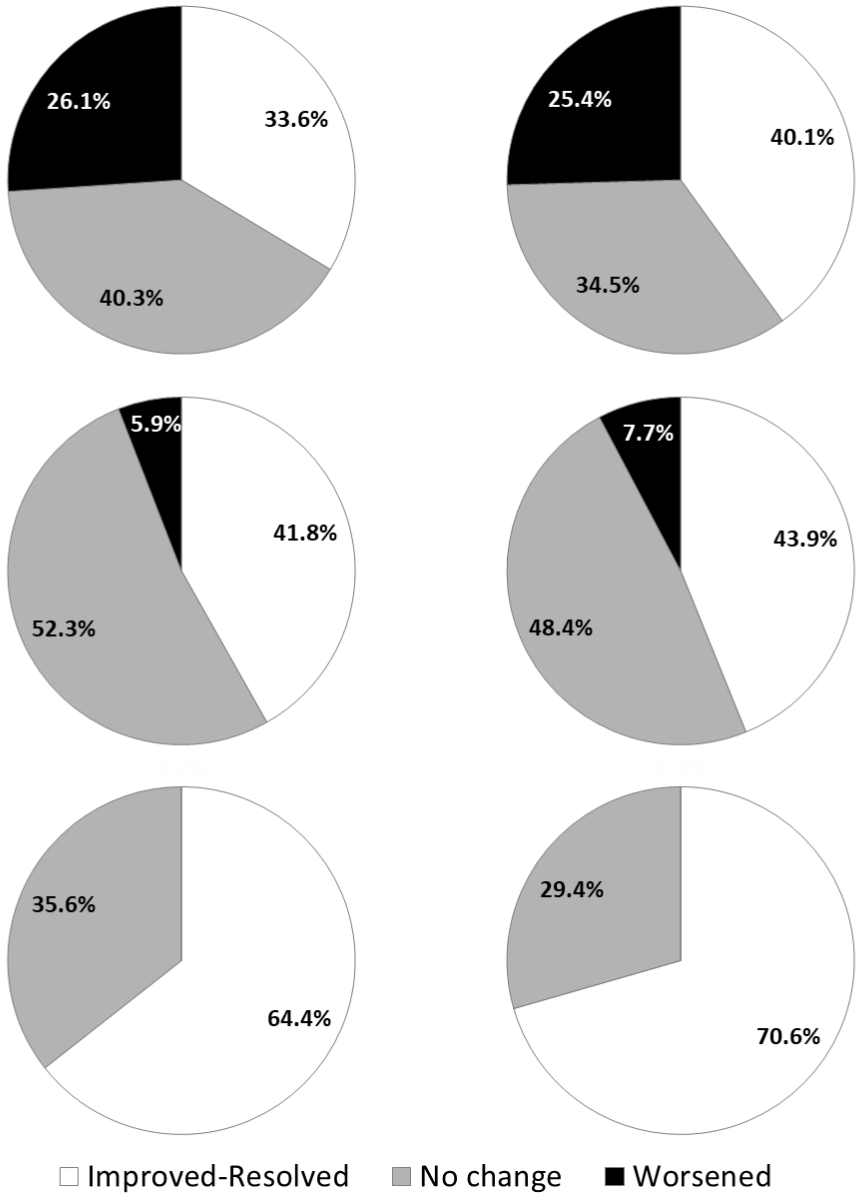

Figure e2. Progression of ARDS severity from first to second day in female and male patients with ARDS invasively ventilated.

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.

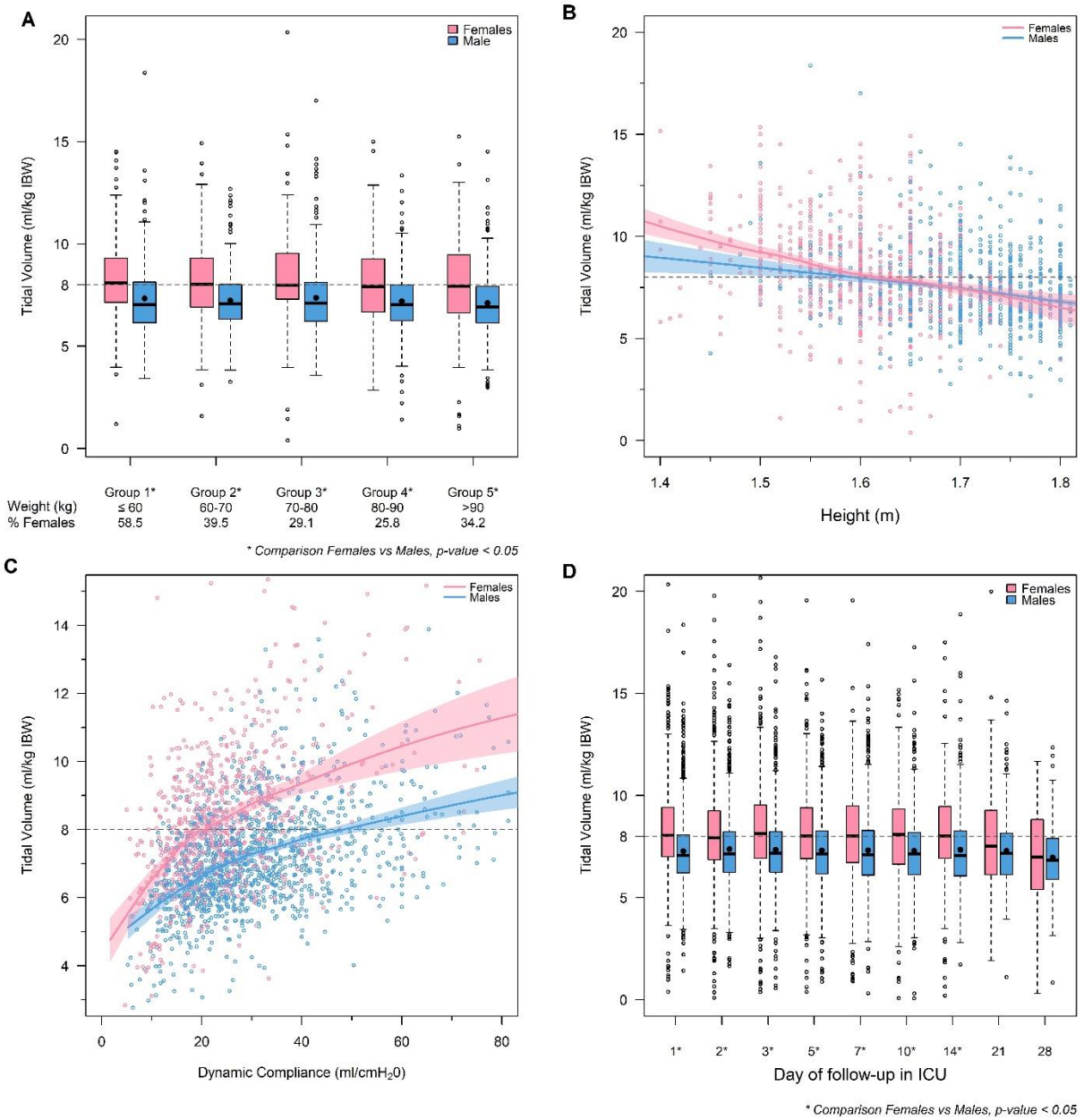

Figure e3. Use of tidal volumes in invasively ventilated female versus male patients with ARDS.

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].

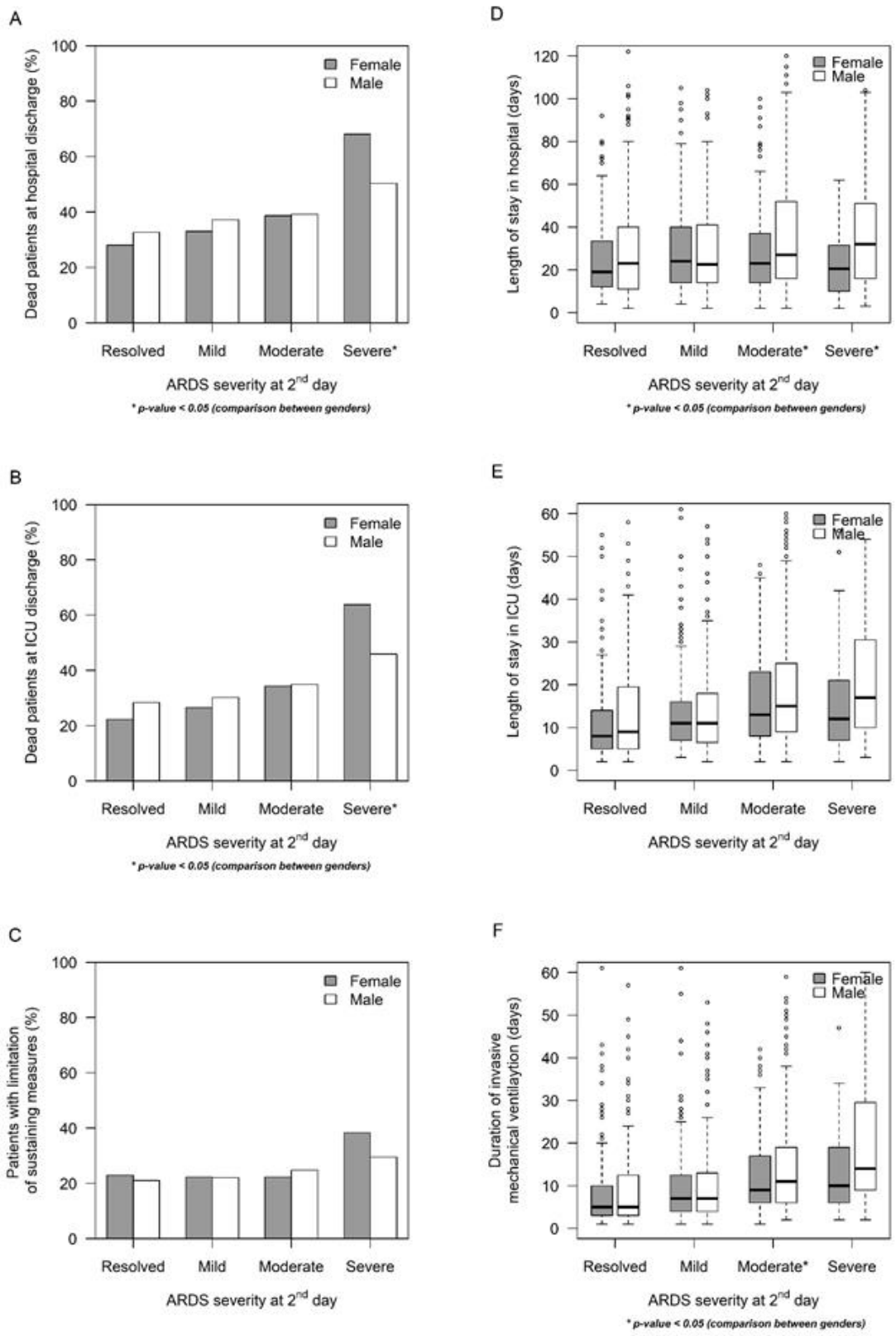

Figure e4. Outcomes in male and female patients stratified by ARDS severity at second day (resolved, mild, moderate and severe).

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

LUNG SAFE national coordinators

Argentina: Fernando Rios; **Australia/New Zealand**: Frank Van Haren; **Belgium:** Sottiaux T, Depuydt P; **Bolivia:** Fredy S Lora; **Brazil:** Luciano Cesar Azevedo; **Canada:** Eddy Fan; **Chile:** Guillermo Bugedo ; **China:** Haibo Qiu; **Colombia**: Marcos Gonzalez; **Costa Rica:** Juan Silesky; **Czech Republic:** Vladimir Cerny; **Denmark:** Jonas Nielsen; **Ecuador:** Manuel Jibaja; **France:** Tài Pham; **Germany:** Hermann Wrigge; **Greece:** Dimitrios Matamis; **Guatemala:** Jorge Luis Ranero; **India:** Pravin Amin; **Iran:** S.M. Hashemian; **Ireland:** Kevin Clarkson; **Italy:** Giacomo Bellani; **Japan:** Kiyoyasu Kurahashi; **Mexico:** Asisclo Villagomez; **Morocco:** Amine Ali Zeggwagh; **Netherlands**: Leo M Heunks; **Norway**: Jon Henrik Laake ; **Philippines:** Jose Emmanuel Palo ; **Portugal:** Antero do Vale Fernandes; **Romania:** Dorel Sandesc; **Saudi Arabia:** Yaasen Arabi; **Serbia:** Vesna Bumbasierevic; **Spain**: Nicolas Nin, Jose A Lorente; **Sweden**: Anders Larsson; **Switzerland**: Lise Piquilloud; **Tunisia**: Fekri Abroug; **United Kingdom:** Daniel F McAuley, Lia McNamee; **Uruguay**: Javier Hurtado; **USA**: Ed Bajwa; **Venezuela:** Gabriel Démpaire;

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.

STUDY COORDINATION: Guy M Francois (European Society of Intensive Care Medicine, Brussels, Belgium)

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