Supplementary file

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e-Methods 1

LUNG-SAFE Study Design and Data Collection

All patients admitted to an ICU (including inter-ICU transfers) within a four-week enrolment window during winter who received invasive or non-invasive ventilation were included. Exclusion criteria were patients younger than 16 years of age or inability to obtain informed consent (if required).

Following enrolment, patients were evaluated daily for acute hypoxemic respiratory failure, defined as the concurrent presence of (1) ratio of arterial oxygen tension to inspired fraction of oxygen of 300mmHg or less; (2)new pulmonary parenchymal abnormalities on chest x-ray or computed tomography; and (3) ventilatory support with continuous positive airway pressure (CPAP), expiratory positive airway pressure (EPAP), or positive end-expiratory pressure (PEEP) of 5 cmH2O or more.

Day 1 was defined as the first day that acute hypoxemic respiratory failure criteria were met, irrespective of ICU admission date. Patient baseline demographics were collected on day 1. An expanded dataset was provided for days 1, 2, 3, 5, 7, 10, 14, 21, and 28 or at ICU discharge or death.

Unless otherwise stated, all data were recorded at the same time – normally as close as possible to 10:00 each day. The following Items were included in the extended dataset*:

- Arterial pH, arterial oxygen tension. arterial carbon dioxide tension, inspired fraction of oxygen and oxygen saturation
- Availability of chest radiography, presence of bilateral opacities and number of involved quadrants
- Mode of ventilatory support (invasive/non-invasive and modality)
- Ventilatory settings including total and set respiratory rate, tidal volume, PEEP, plateau pressure (if available), peak inspiratory pressure, mean airway pressure, oxygen flow
- Use of adjunctive therapies/monitoring in the last 24 hours including prone positioning, recruitment manoeuvres, extra-corporeal membrane oxygenation, high dose corticosteroids, almtrine besylate, continuous sedation, oesophageal pressure monitoring, continuous neuromuscular blocking agents, pulmonary artery catheter, alveolar surfactant, lung

ultrasound, renal replacement therapy, tracheostomy, inhaled vasodilators, neutrophil elastase therapy

- Worst SOFA score over the last 24 hour period

The diagnosis of ARDS in LUNG-SAFE was made by a computer algorithm in the analysis phase of the study using the “raw” data that made up the various components of the Berlin ARDS definition. Patients with ARDS undergoing invasive ventilation were categorized on the day of ARDS diagnosis based on their PaO2/FIO2 ratio into mild (200 <PaO2/FIO2 ≤300 mm Hg), moderate (100 <PaO2/FIO2 ≤200 mm Hg), and severe (PaO2/FIO2 <100 mm Hg).

Patient outcomes included date of liberation from mechanical ventilation and vital status at ICU discharge and at either hospital discharge or at day 90, whichever occurred earlier.

eMethods-2

Predictor variables for assignment of sub-phenotypes in LUNG-SAFE dataset

Predictor variables used in the clinical classifier model used to assign sub-phenotypes in the LUNG-SAFE dataset included; Respiratory Rate (breaths/min), Mean Arterial Pressure (mmHg), Vasopressor Use (yes/no), Platelet Count ($10^3/\mu L$), Creatinine (mg/dL), Bicarbonate (mmol/L), Bilirubin (mg/dL).

eMethods-3

Propensity score matching to reduce imbalance between comparator groups in models 1-4

We used propensity score (PS) matching to improve balance between exposed and control groups; to reduce the impact of confounding. The propensity score is the probability of exposure – in this case to ARDS/AHRF/AHRF-UL – conditional on baseline characteristics.

Exposed and control groups varied in each model, depending on the AF estimate of interest. In model-1, exposed group was patients with ARDS compared to non-AHRF controls; in model-2, exposed group was patients with ARDS compared to AHRF-UL controls; in model-3, exposed group was patients with AHRF compared to non-AHRF controls; and, in model-4, exposed group was patients with AHRF-UL compared to non-AHRF controls.

We estimated propensity scores using logistic regression; and then matched populations using nearest neighbour matching without replacement. Matching without replacement minimises dependence between control and exposed patients, and maximises effect size (and therefore, precision).

The number of matched control units was determined by the size of the selected control population. In model-1, 3, and 4 which used non-AHRF controls (n=8407), we used a 1:2 ratio; In model-2, which used AHRF-UL patients (n = 851) as controls, we used a 1:1 ratio. Each exposed individual (ARDS/AHRF/AHRF-UL, depending on the model) was paired with a control(s) with the smallest propensity score difference.

Selection of matching variables

Matching variables differed by model: predominantly due to availability of data. The LUNG-SAFE study collected a limited dataset for non-AHRF patients; the only potential confounders available for PS matching for these patients – used as controls in Model-1, Model-3 and Model-4 - were age and sex. Data collection for patients with AHRF was more extensive; In Model-2, which compared ARDS patients to AHRF-UL patients, we propensity matched on age, sex, number of comorbidities and receipt of invasive mechanical ventilation. There was no data missing for these variables in the ARDS or AHRF-UL populations. We used a caliper width of +/- 5 years for age: patients with similar propensity scores with a difference in age > 5 years were not matched.

We did not match for illness severity (measured by non-respiratory SOFA score); instead, to account for marginal effects, we included it as a covariate in the logistic regression model used to calculate AF. Graphical representations of each model are shown in eFigure-1.

Assessment of balance and overlap

We assessed balance post matching by estimating standardized mean differences and examining empirical cumulative density function (eCDF) plots for the variables used for matching. We assessed overlap by comparing jitter plots for the matched and unmatched exposed and control groups.

Estimation of AF

We used unconditional logistic regression to calculate AF as we matched on an individual basis without replacement (therefore reducing dependency between cases and controls), and because the size of our dataset meant that we did not have sparse data bias.

We excluded AHRF patients in all four models who were missing data for severity of hypoxaemia, or maximum number of quadrants involved, when estimating AF for these enrichment categories. Sub-phenotype data (hypoinflammatory vs hyperinflammatory) were only available for patients with ARDS.

	Auriemma et al (2020)	Torres et al (2021)	Saha et al (2023)
Data source	Prospective cohort study; EARLI and VALID studies	Prospective cohort study	Prospective cohort study; LUNG-SAFE
Geographical region	United States of America	United States of America South Korea	Multinational
Selected cohort	Mechanically ventilated patients with sepsis	ICU patients with sepsis	Mechanically ventilated patients
Patients with ARDS (n)	EARLI; 195 VALID; 99	141	Model-1; 2653 Model-2; 851
Statistical method to estimate AF	Logistic regression	Survival analysis with targeted minimum loss-based estimation	Logistic regression (in propensity score matched population)
Variables adjusted	Age, sex, race, chronic comorbidities, illness severity (SAPS II/APACHE II/APACHE III), acute comorbidities (shock/pneumonia)	Age, sex, chronic comorbidities, illness severity, invasive mechanical ventilation	Age, sex, chronic comorbidities, illness severity (non-pulmonary SOFA), invasive mechanical ventilation
AF estimate (95% CI)	EARLI; 27% (14 - 37%) VALID; 37% (10 - 51%)	15% (3 - 26%)	Model-1; 38% (34 - 42%) Model-2; 21% (11 - 31%)

eTable-1 Comparison of studies estimating AF_{ARDS}

AF; attributable fraction, ARDS; Acute Respiratory Distress Syndrome, EARLI (Early Assessment of Renal and Lung Injury); VALID (Validating Acute Lung Injury Markers for Diagnosis); LUNG-SAFE; Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure)
Although there are different statistical approaches to estimate AF (see above), we used logistic regression as has been described previously.

	Missing n (%)	
Variable	**ARDS N = 2653**	**AHRF-UL N= 851**
PaO_2:FiO_2 ratio on day 1	1 (0.0)	1 (0.1)
Maximum number of quadrants involved in first 48 hours	-	17 (2.0)
Sub-phenotype	-	851 (100.0)
Non respiratory SOFA score day 1	5 (0.2)	-
Duration of invasive mechanical ventilation	400 (15.1)	150 (17.6)-
Hospital LOS	57 (2.1)	21 (2.5)
Hospital mortality	10 (0.4)	4 (0.5)

eTable-2a. Summary of missing data for ARDS and AHRF patients
Variables excluded from eTable-2a had no missing data. Sub-phenotype data was not available for AHRF-UL patients. There was a low proportion of missing data (<2.0%) for all variables used in our propensity score models and for stratification by enrichment criteria. Duration of invasive mechanical ventilation and hospital LOS were not used as outcomes measures in our analyses.
AHRF- UL: acute hypoxaemic respiratory failure with unilateral infiltrates; ARDS; acute respiratory distress syndrome; FiO_2: inspired fraction of oxygen; ICU: intensive care unit; LOS; length of stay; PaO_2: arterial oxygen tension: SOFA: sequential organ failure assessment

	Non-AHRF controls (N = 8407)
Age (years) Mean (SD)	61.1 (17.2)
Sex Female n (%)	3434 (40.8)
ICU LOS Mean (SD)	6.2 (8.0)
ICU mortality n (%)	1194 (14.0)

eTable-2b. Variables reported for non-AHRF controls
AHRF: acute hypoxaemic respiratory failure; ICU: intensive care unit; LOS: length of stay; SD: standard deviation

Severity of hypoxaemia; PaO_2:FiO_2 (mmHg)	Maximum number of quadrants involved on chest radiograph in first 48 hours		
	Two n (%)	**Three n (%)**	**Four n (%)**
Mild; > 200	394 (51.8)	158 (20.8)	208 (27.4)
Moderate; 100 – 200	499 (39.5)	318 (25.2)	446 (35.3)
Severe; < 100	151 (24.1)	139 (22.2)	336 (53.7)

eTable-3a. Relationship between severity of hypoxaemia and chest radiograph findings in LUNGSAFE cohort.

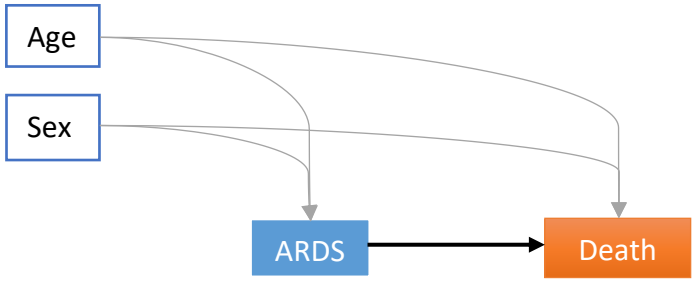
Severity of hypoxaemia; PaO_2:FiO_2 (mmHg)	ARDS sub-phenotype	
	Hypoinflammatory n (%)	**Hyperinflammatory n (%)**
Mild; > 200	581 (76.4)	179 (23.6)
Moderate; 100 – 200	929 (73.6)	334 (26.4)
Severe; < 100	452 (72.2)	174 (27.8)

eTable-3b. Relationship between severity of hypoxaemia and ARDS sub-phenotype in LUNGSAFE cohort
ARDS: acute respiratory distress syndrome

	Model-1 AF_{ARDS}			Model-2 AF_{ARDS}			Model-3 AF_{AHRF}			Model-4 $AF_{AHRF-UL}$		
	ARDS (N=2653)	**Non-AHRF (N= 5306)**	**Std Diff**	**ARDS (N=851)**	**AHRF-UL (N=851)**	**Std Diff**	**AHRF (N=3504)**	**Non-AHRF (N= 7008)**	**Std Diff**	**AHRF-UL (N=851)**	**Non-AHRF (N= 1702)**	**Std Diff**
Age (years) Mean (SD)	61.5 (16.8)	61.4 (16.8)	0.00	63.0 (16.2)	63.0 (16.9)	0.00	61.8 (16.8)	62.0 (16.8)	0.00	63.0 (16.9)	63.0 (16.8)	0.00
Sex Female n (%)	1014 (38.2)	2028 (38.2)	0.00	297 (34.9)	301 (35.4)	-0.01	1315 (37.5)	2664 (38.0)	-0.01	301 (35.4)	599 (35.2)	0.01
Number of comorbidities n (%)												
0	NMV			330 (38.8)	322 (37.8)	0.02	NMV			NMV		
1	NMV			302 (35.5)	302 (35.5)	0.00	NMV			NMV		
2 or more	NMV			219 (25.7)	227 (26.7)	-0.02	NMV			NMV		
Ventilated on day 1 n (%)	NMV			700 (82.3)	698 (82.0)	0.01	NMV			NMV		

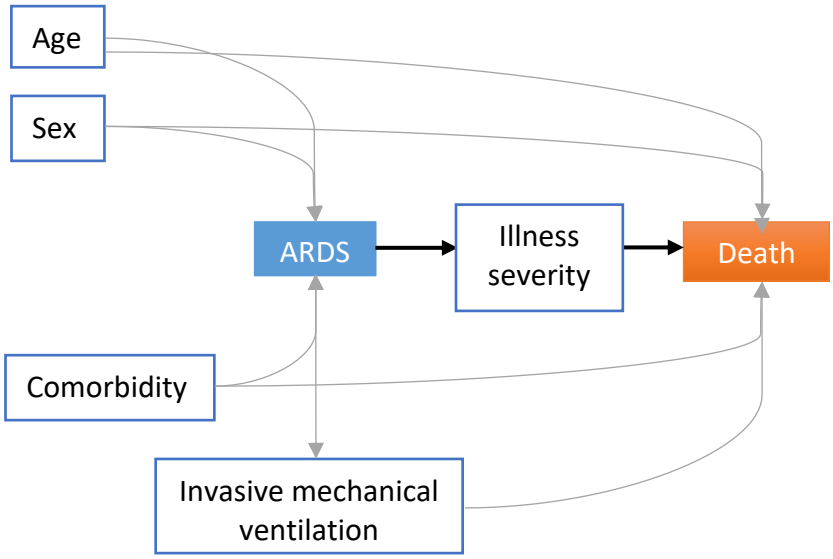
eTable-4 Matching variables for propensity models used to estimate attributable fraction
AF_{ARDS} in Model-1 was estimated by matching 2653 ARDS patients to non-AHRF controls that were propensity score balanced on age and sex in a 1:2 ratio. AF_{ARDS} in Model-2 was estimated by matching 851 ARDS patients to AHRF-UL controls in a 1:1 ratio and propensity score balanced on age, sex, number of comorbidities, and ventilation status on day 1. AF_{AHRF} in Model-3 was estimated by matching 3504 AHRF cases to non-AHRF controls that were propensity score balanced on age and sex in a 1:2 ratio. $AF_{AHRF-UL}$ in Model-4 was estimated by matching 851 AHRF-UL cases to non-AHRF controls that were propensity score balanced on age and sex in a 1:2 ratio.
Mean or proportion (as applicable) are shown for exposed and control populations for each variable. Post matching standardised mean differences (Std Diff) for the matching covariates in each model were all < 0.05. NMV denotes a variable that was not matched for that specific model.
ARDS: acute respiratory distress syndrome; AHRF: acute hypoxaemic respiratory failure; AHRF-UL: acute hypoxaemic respiratory failure with unilateral infiltrates only; Std Diff: standardised mean difference; SD: standard deviation; NMV: non-matched variable.

Model 1: AF_{ARDS} estimate



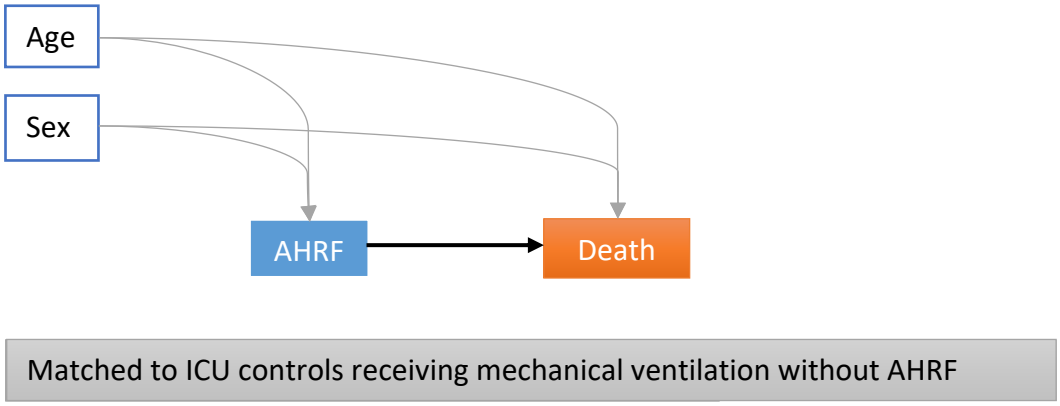
Matched to ICU controls receiving mechanical ventilation without AHRF

Model 2: AF_{ARDS} estimate

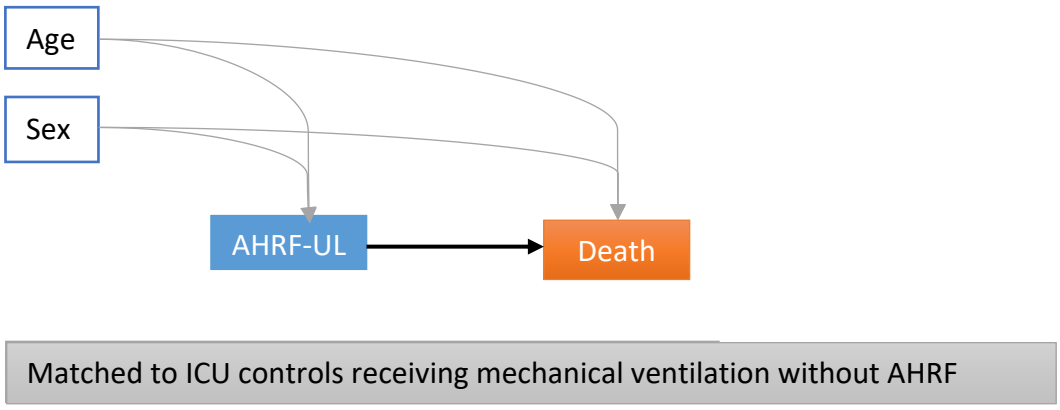


Matched to ICU controls receiving mechanical ventilation with AHRF with unilateral infiltrates only

Model 3: AF_{AHRF} estimate



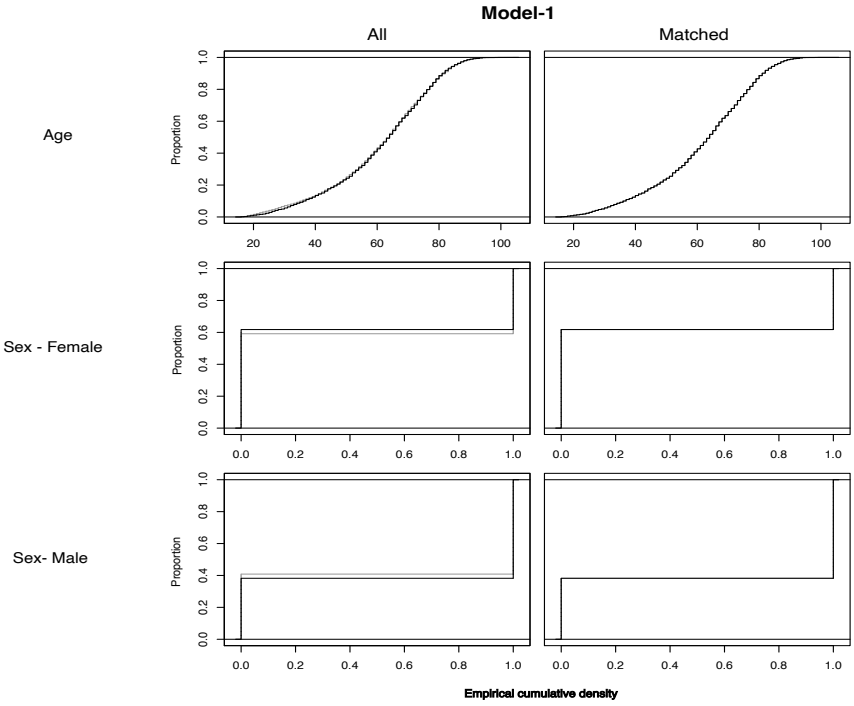
Model 4: $AF_{AHRF\text{-}UL}$ estimate



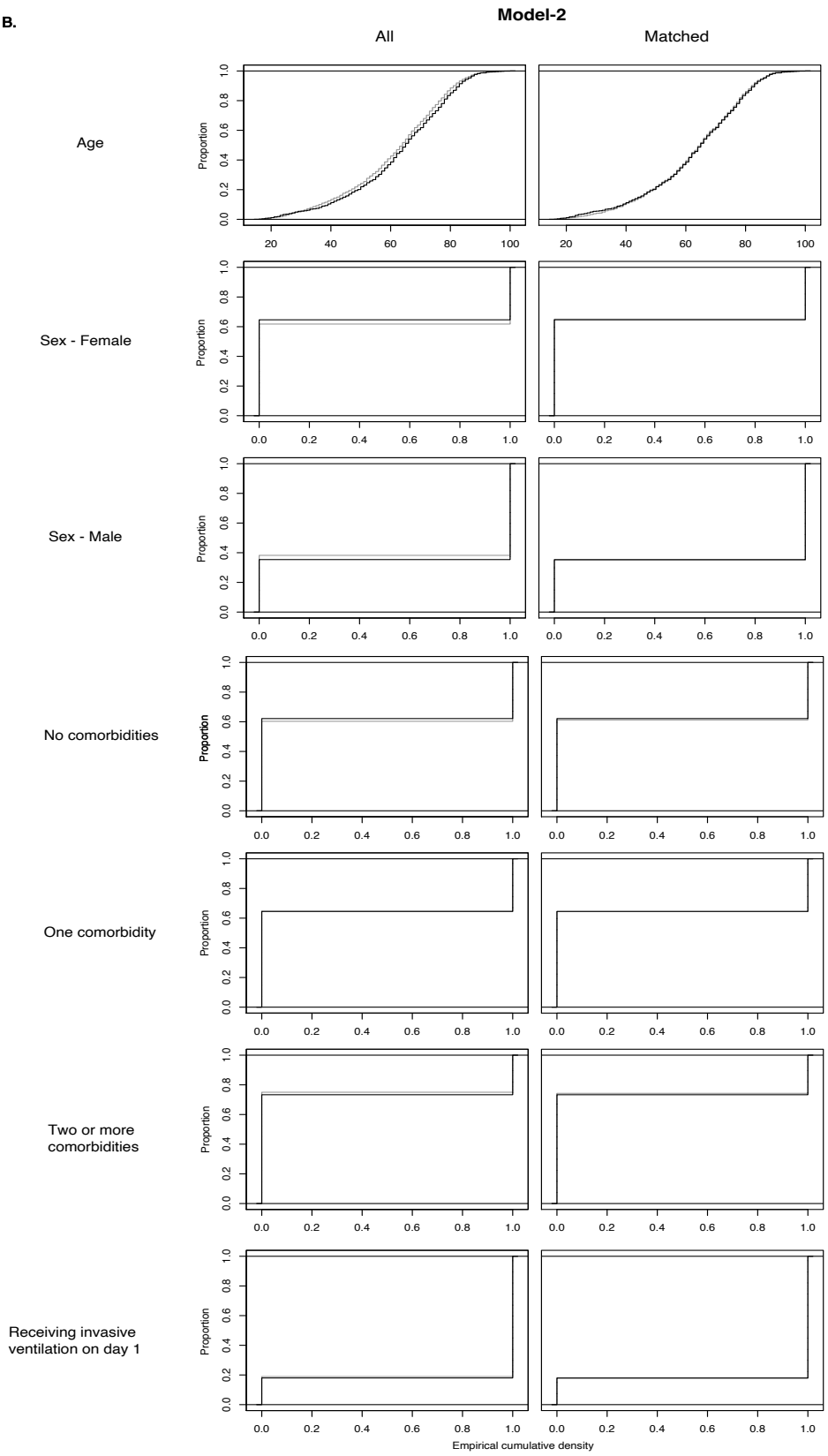
Variable: Exposure | Outcome | Confounder

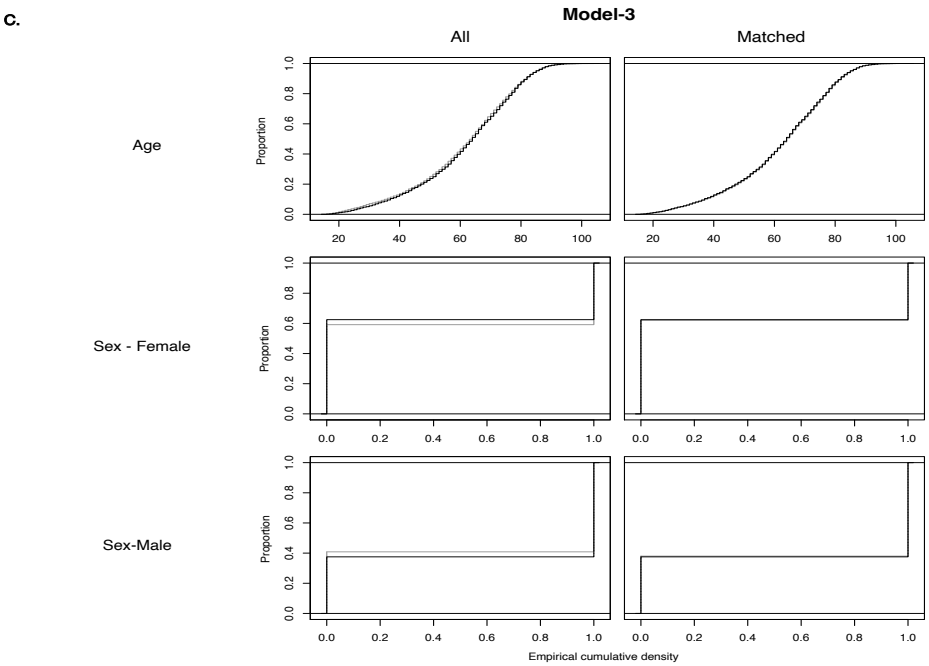
eFigure-1. Matching procedures to generate models to estimate AF
Propensity score matching was used to estimate the effect of the exposure (ARDS/AHRF/AHRF-UL) on ICU mortality while controlling for measured confounding variables. Relationships between exposures, outcomes, and confounding variables for all 4 models used in our analysis are shown in the figure.
As a limited dataset was collected for non-AHRF ICU controls in the LUNG SAFE study, the only potential confounders available for these patients were age and sex. Model-1, Model-3 and Model-4 were propensity matched on age and sex only.
A more extensive dataset was collected for all patients with AHRF. In Model-2, we additionally propensity matched on number of comorbidities and receipt of invasive mechanical ventilation, as well as age and sex. Illness severity (measured by non-respiratory SOFA score) was not matched. Instead, it was included in the regression model as a mediator variable.

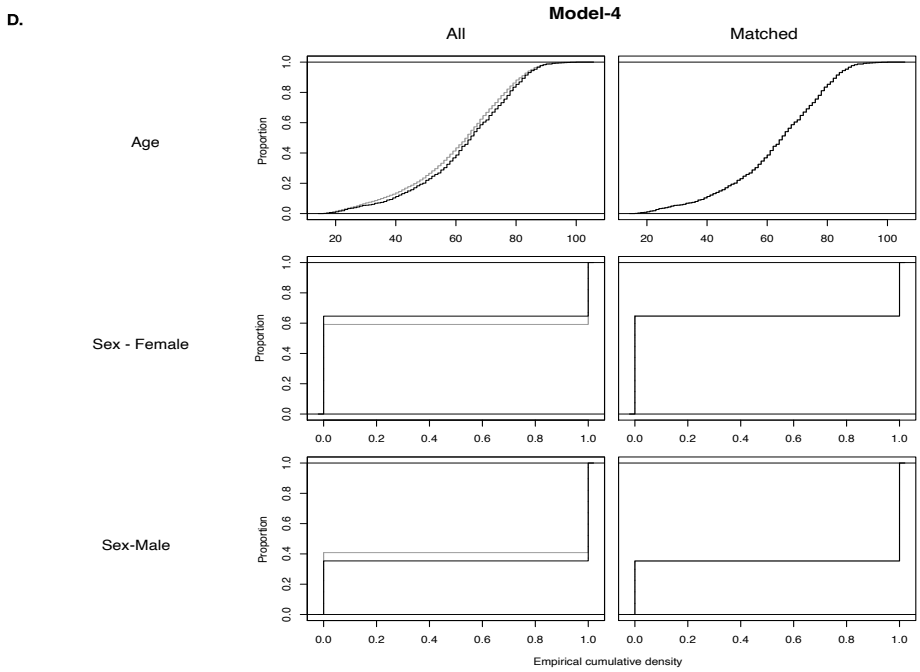
A.


Model-1
All
Matched
Age
Sex - Female
Sex- Male
Proportion
Empirical cumulative density

B.


Model-2
All
Matched
Age
Sex - Female
Sex - Male
No comorbidities
One comorbidity
Two or more comorbidities
Receiving invasive ventilation on day 1
Proportion
Empirical cumulative density





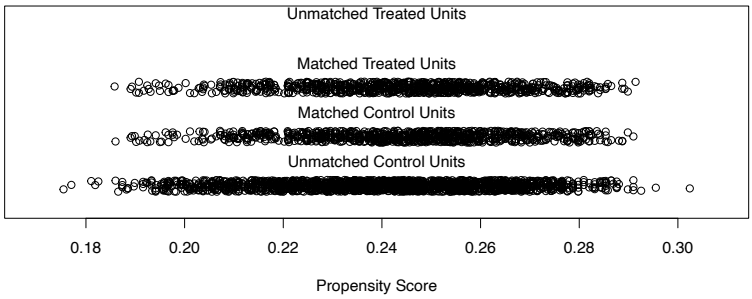
eFigure-2. Assessment of balance post-matching using empirical cumulative density function plots for matching variables.

Empirical cumulative densities for each covariate are displayed on the x-axis and the proportion of the sample at, or less than, the covariate value are displayed on the y-axis. The black line corresponds to exposed group (ARDS/AHRF/AHRF-UL, as applicable) and the grey line to the control group (non-AHRF/AHRF-UL, as applicable). Perfectly overlapping lines indicated good balance. The panel on the left shows balance pre-matching; the panel on the right shows balance post-matching.

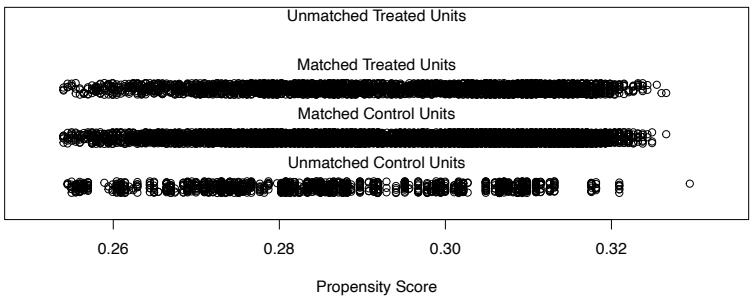
A. Covariates used for matching in model-1: ARDS vs non-AHRF controls; B. Covariates used for matching in model-2: ARDS vs AHRF-UL controls; C. Covariates used for matching in model-3: AHRF vs non-AHRF controls; D. Covariates used for matching in model-4: AHRF-UL vs non-AHRF controls.

Model 1: ARDS vs non-AHRF controls

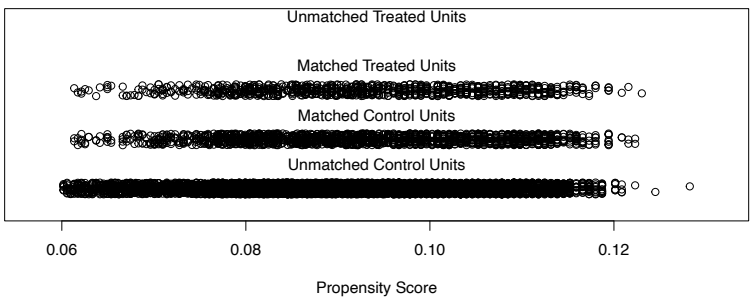
Model 2: ARDS vs AHRF controls



Model 3: AHRF vs non-AHRF controls



Model 4: AHRF-UL vs non-AHRF controls



eFigure-3. Assessment of overlap post-matching using jitter plots to compare propensity scores for matched and unmatched control/treatment groups.