Original research

Estimating the attributable fraction of mortality from acute respiratory distress syndrome to inform enrichment in future randomised clinical trials

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ABSTRACT

Background Efficiency of randomised clinical trials of acute respiratory distress syndrome (ARDS) depends on the fraction of deaths attributable to ARDS (AFARDS) to which interventions are targeted. Estimates of AFARDS in subpopulations of ARDS could improve design of ARDS trials.

Methods We performed a matched case-control study using the Large observational study to Understand the Global impact of Severe Acute Respiratory Failure cohort. Primary outcome was intensive care unit mortality. We used nearest neighbour propensity score matching without replacement to match ARDS to non-ARDS populations. We derived two separate AFARDS estimates by matching patients with ARDS to patients with non-acute hypoxaemic respiratory failure (non-AHRF) and to patients with AHRF with unilateral infiltrates only (AHRF-UL). We also estimated AFARDS in subgroups based on severity of hypoxaemia, number of lung quadrants involved and hyperinflammatory versus hypoinflammatory phenotypes. Additionally, we derived AFARDS estimates by matching patients with AHRF to non-AHRF controls, and AFARDS-UL estimates by matching patients with AHRF-UL to non-AHRF controls.

Results Estimated AFARDS was 20.9% (95% CI 10.5% to 31.4%) when compared with AHRF-UL controls and 38.8% (95% CI 34.4% to 41.6%) compared with non-AHRF controls. Within subgroups, estimates for AFARDS compared with AHRF-UL controls were highest in patients with severe hypoxaemia (41.1% (95% CI 25.2% to 57.1%)), in those with four quadrant involvement on chest radiography (28.9% (95% CI 13.4% to 44.3%)) and in the hyperinflammatory subphenotype (26.8% (95% CI 6.9% to 46.7%)). Estimated AFARDS was 33.8% (95% CI 30.5% to 37.1%) compared with non-AHRF controls. Estimated AFARDS was 21.3% (95% CI 312.8% to 29.7%) compared with non-AHRF controls.

Conclusions Overall AFARDS mean values were between 20.9% and 38.0%, with higher AFARDS seen with severe hypoxaemia, four quadrant involvement on chest radiography and hyperinflammatory ARDS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The excess mortality—or attributable fraction (AF)—due to acute respiratory distress syndrome (ARDS) has been estimated to range between 15% and 37%.

⇒ We do not know how this varies by severity of hypoxaemia, radiographic findings and ARDS subphenotype.

WHAT THIS STUDY ADDS

⇒ We observed a dose-response increase in AFARDS with severity of hypoxaemia, quadrants of radiographic involvement and that AFARDS was higher in the hyperinflammatory compared with the hypoinflammatory subphenotype of ARDS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We highlight ARDS subpopulations that can inform enrichment options in randomised clinical trials.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) refers to acute hypoxaemic respiratory failure (AHRF) occurring within 1 week of a known clinical insult, with bilateral opacities on chest radiography that are not fully explained by effusions, lobar/lung collapse or nodules.1 Treatments with biological plausibility2 and strong supporting preclinical evidence, when tested within randomised clinical trials (RCTs),3 often report statistically indeterminate results (ie, uncertainty highlighted by non-significant results of two-tailed tests, rather than proof of no difference between treatments (negative)4). Addressing this issue remains a major clinical and methodological challenge.2

There are several explanations for statistically indeterminate RCT results, aside from testing of ineffective treatments. First, as ARDS is a heterogeneous syndrome, RCTs may consist of participants who either benefit, have no effect or are harmed by the tested intervention. This explanation is supported by observations that distinct subphenotypes of ARDS respond differently to treatments.2,5 Second, there are several design issues within ARDS RCTs. This explanation is supported by observations that sample size calculations
overestimate control arm event rates, and the expected average treatment effect.\textsuperscript{12}

In this manuscript, we explore another explanation—variation in the excess fraction of mortality attributable to ARDS (AF\textsubscript{ARDS})\textsuperscript{13,14} in RCT participants. Patients with ARDS may die from ARDS (ie, AF\textsubscript{ARDS}) or with ARDS (ie, death may be due to risk factors like comorbidities and/or other organ dysfunction during critical illness). If we explicitly link the eligibility criteria of ARDS RCTs to AF\textsubscript{ARDS} estimates (ie, the excess proportion of deaths from ARDS), then efficiency of ARDS RCTs would be increased from the generic predictive and prognostic enrichment alongside increase in average treatment effect. We hypothesised that AF\textsubscript{ARDS} will vary by severity of hypoxaemia as per the Berlin ARDS definitions,\textsuperscript{15} by number of quadrants affected on chest radiography,\textsuperscript{16} and by subphenotype. Our hypothesis was informed by the following observations: first, two small cohort studies (online supplemental eTable 1) indicated that AF\textsubscript{ARDS} ranges between 15\% and 37\%.\textsuperscript{17,18} second, in the Berlin ARDS definitions, ARDS outcomes worsened with increasing severity of hypoxaemia.\textsuperscript{3} Third, the inflammatory ARDS subphenotype had higher mortality and greater treatment effect within RCTs.\textsuperscript{5-11} Recently, these ARDS subphenotypes were identified within the Large observational study to Understand the Global impact of Severe Acute respiratory Failure (LUNG-SAFE) cohort using machine learning models,\textsuperscript{19} are available as predefined categories within the LUNG-SAFE dataset and currently there are no AF\textsubscript{ARDS} estimates for them. Given recent proposals to include patients with AHRF (including those with unilateral infiltrates\textsuperscript{20}) within an expanded ARDS case definition,\textsuperscript{21} we also compared AF\textsubscript{AHRF} and AF\textsubscript{ARDS}.

METHODS

Data source

Our data source was the well-described LUNG-SAFE dataset. We summarise key elements of the LUNG-SAFE study design and data collection in online supplemental eMethods 1. National coordinators and site investigators of the LUNG-SAFE study are listed in the online supplemental file 1. AHRF was defined as concurrent presence of: (a) arterial oxygen tension:inspired fraction of oxygen (\text{PaO}_2:FiO_2) ratio \leq 300 mm Hg; (b) new pulmonary parenchymal abnormalities (either unilateral or bilateral) on chest radiography and (c) ventilatory support with continuous positive airway pressure or expiratory positive airway pressure or positive end expiratory pressure \geq 5 cmH\text{O}. The diagnosis of ARDS in LUNG-SAFE studies 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.\textsuperscript{12}

STUDY POPULATION

Selection criteria of AHRF/ARDS cohort reported in this manuscript were described previously by Pham et al.\textsuperscript{20} We defined four populations for our matched cohort study, after excluding patients with congestive heart failure: (1) patients with ARDS-AHRF who met the Berlin ARDS criteria, (2) patients with AHRF who met criteria for AHRF (and therefore includes all patients with ARDS), (3) patients with AHRF with unilateral infiltrates (AHRF-UL)—meet criteria for AHRF but not ARDS and (4) non-AHRF controls—patients receiving non-invasive or invasive ventilation who did not meet criteria for AHRF (figure 1). The LUNG-SAFE study collected only the following variables for non-AHRF controls—age, sex, intensive care unit (ICU) length of stay and ICU mortality.

ARDS subphenotypes have recently been assigned in the LUNG-SAFE cohort using a clinical classifier model with a limited selection of predictor variables\textsuperscript{19} (online supplemental eMethods 2). Of note, this model used optimised probability cutoffs and did not use latent class analysis to assign subphenotypes. Patients without ARDS do not have subphenotype allocation.

There were no patients who had unilateral infiltrates without AHRF, to act as controls for AF\textsubscript{AHRF} range estimates, similar to the AF\textsubscript{ARDS} range estimates we report.

ANALYSES FRAMEWORK

The primary exposure was either ARDS, or AHRF, or AHRF-UL. The primary outcome was ICU mortality, as one of the most reported outcomes in ARDS RCTs.\textsuperscript{3} Predefined enrichment categories within the primary exposures were severity of hypoxaemia, number of quadrants affected on chest radiography and subphenotypes. Due to the low proportion of missing data (online supplemental eTable 2a), without any discernible pattern of missingness, these data were assumed to be missing at random, and complete-case analyses were used for all models.

Estimation of AF\textsubscript{ARDS} requires careful selection of controls and consideration of potential confounding variables. We estimated propensity scores for the exposures using logistic regression. We used nearest neighbour matching without replacement to match exposed patients to controls. With this approach, the mortality in the control groups within each prespecified ARDS severity category (severity of hypoxaemia, radiology and subphenotype) would also vary based on matching, enabling estimation of variation in AF\textsubscript{ARDS} within these categories, along with AF\textsubscript{ARDS}.

Propensity score models and scenarios

Model 1 scenario

AF\textsubscript{ARDS} could be reduced with treatment to mortality seen in ICU patients of similar age and sex without AHRF (one patient with ARDS was matched to two non-AHRF controls).

Model 2 scenario

AF\textsubscript{ARDS} could be reduced with treatment to mortality seen in ICU patients with AHRF after accounting for variables commonly considered as part of eligibility criteria in ARDS RCTs at the time of randomisation such as age, sex, number of comorbidities, receipt of invasive mechanical ventilation and illness severity (one patient with ARDS was matched to one AHRF-UL control).

Model 3 scenario

AF\textsubscript{AHRF} could be reduced with treatment to mortality seen in ICU patients of similar age and sex without AHRF (one patient with AHRF was matched to two non-AHRF controls).

Model 4 scenario

AF\textsubscript{AHRF-UL} could be reduced with treatment to mortality seen in ICU patients of similar age and sex without AHRF scenario (one patient with AHRF-UL was matched to two non-AHRF controls).

Additional rationale for matching methods, covariate selection and assessment of each of four different propensity score models are available in figure 1, online supplemental eMethods 3 and online supplemental eFigure 1.

We used four separate logistic regression models to estimate AF (AF\textsubscript{ARDS}, AF\textsubscript{AHRF}, AF\textsubscript{AHRF-UL}).
Estimation of AFARDS range
We used model 1 and model 2 to estimate the variation in AFARDS by severity of hypoxaemia categories (mild (PaO$_2$:FiO$_2$ > 200 mm Hg); moderate (PaO$_2$:FiO$_2$ 100–200 mm Hg) or severe (PaO$_2$:FiO$_2$ < 100 mm Hg)); the number of quadrants involved radiographically in the first 48 hours after ICU admission (two, three or four), and the hyperinflammatory versus hypoinflammatory ARDS subphenotypes within LUNG-SAFE dataset.

Estimation of AF_AHRF
We used model 3 to estimate the variation in AF_AHRF by severity of hypoxaemia categories (mild, moderate, severe), and the number of quadrants involved radiographically in the first 48 hours after ICU admission (two, three or four).

Estimation of AF_AHRF-UL
We used model 4 to estimate the variation in AF_AHRF-UL by severity of hypoxaemia categories (mild, moderate, severe), and the number of quadrants involved radiographically in the first 48 hours after ICU admission (one, two).

Simulating AFARDS-based sample size estimates for different enrichment subgroups
To illustrate how AFARDS can influence sample size estimation, we compared predicted sample size estimates from 28 published ARDS RCTs that used mortality as primary outcome (identified in our previous systematic review) to simulated sample size estimates. We simulated sample size calculations for the scenario where AFARDS = 100%, and for estimates of AFARDS from model 1 stratified by severity of hypoxaemia (mild, moderate or severe), maximum number of quadrants involved on chest radiography at 48 hours (two, three or four) and (c) subphenotype of ARDS (hyperinflammatory or hypoinflammatory). For all simulations, RCT control event rate was fixed at 40%, alpha at 0.05 and power at 0.80.
Table 1  Baseline characteristics of ARDS, AHRF, AHRF-UL and corresponding propensity matched control populations to derive attributable fraction

<table>
<thead>
<tr>
<th></th>
<th>Model 1 AFARDS (n=2653)</th>
<th>Non-AHRF (n=5306)</th>
<th>Model 2 AFARDS (n=851)</th>
<th>AHRF-UL (n=851)</th>
<th>Model 3 AFARDS (n=3504)</th>
<th>Non-AHRF (n=7008)</th>
<th>Model 4 AFARDS (n=851)</th>
<th>AHRF-UL (n=851)</th>
<th>Non-AHRF (n=1702)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>61.5 (16.8)</td>
<td>61.4 (16.8)</td>
<td>63.0 (16.2)</td>
<td>63.0 (16.9)</td>
<td>61.8 (16.8)</td>
<td>62.0 (16.8)</td>
<td>63.0 (16.9)</td>
<td>63.0 (16.8)</td>
<td>63.0 (16.8)</td>
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<tr>
<td>Sex—female n (%)</td>
<td>1014 (38.2)</td>
<td>2028 (38.2)</td>
<td>297 (34.9)</td>
<td>301 (35.4)</td>
<td>1315 (37.5)</td>
<td>2664 (38.0)</td>
<td>301 (35.4)</td>
<td>599 (35.2)</td>
<td></td>
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<tr>
<td>BMI mean (SD)</td>
<td>27.4 (8.6)</td>
<td>–</td>
<td>26.9 (7.3)</td>
<td>26.7 (6.8)</td>
<td>27.3 (8.2)</td>
<td>–</td>
<td>26.7 (6.8)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Number of comorbidities n (%)</td>
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<tr>
<td>0</td>
<td>1053 (39.7)</td>
<td>–</td>
<td>330 (38.8)</td>
<td>322 (37.8)</td>
<td>1375 (39.2)</td>
<td>322 (37.8)</td>
<td>–</td>
<td>322 (37.8)</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>937 (35.3)</td>
<td>–</td>
<td>302 (35.5)</td>
<td>302 (35.5)</td>
<td>1239 (35.4)</td>
<td>302 (35.5)</td>
<td>–</td>
<td>302 (35.5)</td>
<td>–</td>
</tr>
<tr>
<td>2 or more</td>
<td>663 (25.0)</td>
<td>–</td>
<td>219 (25.7)</td>
<td>227 (26.7)</td>
<td>890 (25.4)</td>
<td>–</td>
<td>227 (26.7)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Risk factor for ARDS n (%)</td>
<td></td>
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<tr>
<td>Pneumonia</td>
<td>1574 (59.3)</td>
<td>–</td>
<td>510 (59.9)</td>
<td>433 (50.9)</td>
<td>2007 (57.3)</td>
<td>–</td>
<td>433 (50.9)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Extrapulmonary sepsis</td>
<td>421 (15.9)</td>
<td>–</td>
<td>141 (16.6)</td>
<td>115 (13.5)</td>
<td>536 (15.3)</td>
<td>–</td>
<td>115 (13.5)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Aspiration</td>
<td>386 (14.5)</td>
<td>–</td>
<td>114 (13.4)</td>
<td>157 (18.4)</td>
<td>543 (15.5)</td>
<td>–</td>
<td>157 (18.4)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Pancreatitis</td>
<td>57 (2.1)</td>
<td>–</td>
<td>16 (1.9)</td>
<td>11 (1.3)</td>
<td>68 (1.9)</td>
<td>–</td>
<td>11 (1.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary vasculitis</td>
<td>12 (0.5)</td>
<td>–</td>
<td>2 (0.2)</td>
<td>0 (0)</td>
<td>12 (0.3)</td>
<td>–</td>
<td>0 (0.0)</td>
<td>–</td>
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</tr>
<tr>
<td>Trauma</td>
<td>108 (4.1)</td>
<td>–</td>
<td>37 (4.3)</td>
<td>48 (5.6)</td>
<td>156 (4.5)</td>
<td>–</td>
<td>48 (5.6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Inhalation</td>
<td>69 (2.6)</td>
<td>–</td>
<td>28 (3.3)</td>
<td>22 (2.6)</td>
<td>91 (2.6)</td>
<td>–</td>
<td>22 (2.6)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Pulmonary contusion</td>
<td>82 (3.1)</td>
<td>–</td>
<td>28 (3.3)</td>
<td>34 (4.0)</td>
<td>116 (3.3)</td>
<td>–</td>
<td>34 (4.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Burns</td>
<td>7 (0.3)</td>
<td>–</td>
<td>3 (0.4)</td>
<td>2 (0.2)</td>
<td>9 (0.3)</td>
<td>–</td>
<td>2 (0.2)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Non-cardiogenic shock</td>
<td>201 (7.6)</td>
<td>–</td>
<td>75 (8.8)</td>
<td>52 (6.1)</td>
<td>253 (7.2)</td>
<td>–</td>
<td>52 (6.1)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Drowning</td>
<td>2 (0.1)</td>
<td>–</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>2 (0.1)</td>
<td>–</td>
<td>0 (0.0)</td>
<td>–</td>
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<tr>
<td>Drug overdose</td>
<td>47 (1.8)</td>
<td>–</td>
<td>11 (1.3)</td>
<td>22 (2.6)</td>
<td>69 (2.0)</td>
<td>–</td>
<td>22 (2.6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Transfusion-related</td>
<td>107 (4.0)</td>
<td>–</td>
<td>34 (4.0)</td>
<td>27 (3.2)</td>
<td>134 (3.8)</td>
<td>–</td>
<td>27 (3.2)</td>
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</tr>
<tr>
<td>Other</td>
<td>67 (2.5)</td>
<td>–</td>
<td>17 (2.0)</td>
<td>45 (5.3)</td>
<td>112 (3.2)</td>
<td>–</td>
<td>45 (5.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>No risk factor for ARDS</td>
<td>229 (8.6)</td>
<td>–</td>
<td>79 (9.3)</td>
<td>0 (0)</td>
<td>229 (6.5)</td>
<td>–</td>
<td>0 (0.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PaO2:FiO2 ratio on day 1 mean (SD)*</td>
<td>159 (67.4)</td>
<td>–</td>
<td>161 (67.6)</td>
<td>188 (63.6)</td>
<td>166 (67.8)</td>
<td>–</td>
<td>188 (63.6)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Severity of hypoxaemia on day 1 n (%)</td>
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<tr>
<td>Mild (200–300)</td>
<td>760 (28.6)</td>
<td>–</td>
<td>249 (29.3)</td>
<td>377 (44.3)</td>
<td>1137 (32.4)</td>
<td>–</td>
<td>377 (44.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Moderate (100–200)</td>
<td>1263 (47.6)</td>
<td>–</td>
<td>400 (47.0)</td>
<td>380 (44.7)</td>
<td>1643 (46.9)</td>
<td>–</td>
<td>380 (44.7)</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Severe (&lt;100)</td>
<td>626 (23.6)</td>
<td>–</td>
<td>200 (23.5)</td>
<td>93 (10.9)</td>
<td>719 (20.5)</td>
<td>–</td>
<td>93 (10.9)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Maximum number of quadrants involved in first 48 hours n (%)*</td>
<td></td>
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<tr>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>596 (70.2)</td>
<td>482 (13.8)</td>
<td>–</td>
<td>482 (70.2)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>1045 (39.4)</td>
<td>–</td>
<td>351 (41.2)</td>
<td>236 (27.7)</td>
<td>1281 (36.6)</td>
<td>–</td>
<td>236 (27.7)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>615 (23.2)</td>
<td>–</td>
<td>214 (25.1)</td>
<td>624 (71.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>993 (37.4)</td>
<td>–</td>
<td>286 (33.6)</td>
<td>–</td>
<td>1000 (28.5)</td>
<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>
AFARDS in model 1 was estimated by matching 2653 patients with ARDS to non-AHRF controls that were propensity score balanced on age and sex in a 1:2 ratio. AFARDS in model 2 was estimated by matching 851 patients with ARDS 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. AFAHRF 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. AFAHRF-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.

Postmatching standardised mean differences for the matching covariates in each model are shown in online supplemental eTable 2a. AF, attributable fraction; AHRF, acute hypoxaemic respiratory failure; AHRF-UL, acute hypoxaemic respiratory failure with unilateral infiltrates only; ARDS, acute respiratory distress syndrome; BMI, body mass index; ICU, intensive care unit; LOS, length of stay; NMV, non-matched variable; PaO2:FiO2, arterial oxygen tension:inspired fraction of oxygen; SOFA, Sequential Organ Failure Assessment.

**Table 1** Continued

<table>
<thead>
<tr>
<th>Model 1 AF(_{\text{ARDS}})</th>
<th>Model 2 AF(_{\text{ARDS}})</th>
<th>Model 3 AF(_{\text{AHRF}})</th>
<th>Model 4 AF(_{\text{AHRF-UL}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS (n=2653)</td>
<td>Non-AHRF (n=5306)</td>
<td>ARDS (n=851)</td>
<td>AHRF-UL (n=851)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AHRF (n=3504)</td>
<td>Non-AHRF (n=7008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AHRF-UL (n=851)</td>
<td>Non-AHRF (n=1702)</td>
</tr>
<tr>
<td><strong>Subphenotype of ARDS n (%)</strong></td>
<td><strong>Subphenotype of ARDS n (%)</strong></td>
<td><strong>Subphenotype of ARDS n (%)</strong></td>
<td><strong>Subphenotype of ARDS n (%)</strong></td>
</tr>
<tr>
<td>Hypoinflammatory</td>
<td>1966 (74.1) –</td>
<td>616 (72.4) –</td>
<td>–</td>
</tr>
<tr>
<td>Hyperinflammatory</td>
<td>687 (25.9) –</td>
<td>235 (27.6) –</td>
<td>–</td>
</tr>
<tr>
<td>SOFA score day 1 mean (SD)</td>
<td>9.39 (4.08) –</td>
<td>9.55 (4.19) –</td>
<td>8.69 (3.97) –</td>
</tr>
<tr>
<td>Non-respiratory SOFA score day 1*</td>
<td>6.48 (3.96) –</td>
<td>6.65 (4.06) –</td>
<td>6.4 (3.87) –</td>
</tr>
<tr>
<td>Ventilated on day 1 n (%)</td>
<td>2151 (81.1) –</td>
<td>700 (82.3) –</td>
<td>2849 (81.3) –</td>
</tr>
<tr>
<td>Duration of invasive mechanical ventilation mean (SD)*</td>
<td>12.0 (12.9) –</td>
<td>12.2 (12.8) –</td>
<td>10.6 (12.6) –</td>
</tr>
<tr>
<td>ICU LOS mean (SD)</td>
<td>14.2 (14.0) –</td>
<td>12.7 (13.8) –</td>
<td>13.8 (14.0) –</td>
</tr>
<tr>
<td>ICU mortality n (%)</td>
<td>906 (34.2) –</td>
<td>293 (34.4) –</td>
<td>1112 (31.7) –</td>
</tr>
<tr>
<td>Hospital LOS mean (SD)*</td>
<td>23.1 (20.8) –</td>
<td>23.6 (20.7) –</td>
<td>22.9 (20.8) –</td>
</tr>
<tr>
<td>Hospital mortality n (%)*</td>
<td>1044 (39.4) –</td>
<td>342 (40.2) –</td>
<td>259 (30.4) –</td>
</tr>
</tbody>
</table>

AF\(_{\text{ARDS}}\) in model 1 was estimated by matching 2653 patients with ARDS to non-AHRF controls that were propensity score balanced on age and sex in a 1:2 ratio. AF\(_{\text{ARDS}}\) in model 2 was estimated by matching 851 patients with ARDS 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\(_{\text{AHRF}}\) 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\(_{\text{AHRF-UL}}\) 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.

*Denotes variable with missing data. Further details of missing data are available in online supplemental eTable 2a.
Critical care

We report the following sensitivity analyses: (i) unmatched analyses in all four models to assess how matching—and therefore, exclusion of controls—affected overall and subpopulation estimates and (ii) used hospital mortality as outcome measure in model 2—instead of ICU mortality—to assess how choice of mortality timepoint affected overall and subpopulation estimates for AFARDS.

The χ² test was used to assess linear trends in ICU mortality across subpopulations, and to assess relationship between enrichment categories. Reported p values are two-sided and p values <0.05 were considered statistically significant. All analyses were performed using R V3.4.2 (AF, 50 Matchit 51 and tidyverse 52 packages).

RESULTS

Among 12,906 admissions who received ventilatory support in the ICU, we identified 3,504 eligible patients with AHRF; 2,653 met the Berlin ARDS criteria and 851 patients had AHRF-UL (figure 1). Missing data are summarised in online supplemental eTable 2a. Baseline characteristics and outcomes for patients with non-AHRF are summarised in online supplemental eTable 2b. Patients with mild hypoxaemia most often had two quadrant infiltrates, while patients with severe hypoxaemia had four quadrant infiltrates (online supplemental eTable 3a). There was no association between severity of hypoxaemia and ARDS subphenotype (online supplemental eTable 3b).

Model 1 scenario

Model 1 scenario compared 2,653 patients with ARDS matched to 5,306 non-AHRF controls. Patients with ARDS had higher ICU mortality compared with controls (34.8% vs 13.8%) (table 1). Significant linear trends in mortality were seen with severity of hypoxaemia category (mild 28.6% vs 13.2%; moderate 33.2% vs 14.6%; severe 43.0% vs 13.1%; χ²=32.7; p<0.001); and with increase in number of quadrants involved (two quadrants 27.7% vs 14.4%; three quadrants 34.7% vs 14.7%; four quadrants 40.6% vs 12.7%; χ²=90.9; p<0.001). The ICU mortality was higher for hyperinflammatory (51.7% vs 12.4%) and hypoinflammatory (28.0% vs 14.4%) ARDS, compared with non-AHRF controls (χ²=413.07; p<0.001).

Model 2 scenario

Model 2 scenario compared 851 patients with ARDS with 851 AHRF-UL controls. Patients with ARDS had higher ICU mortality (34.4% vs 24.2%; p<0.001), with the higher control arm mortality compared with model 1 reflecting the differences in mortality risk between ICU and hospital settings.
Critical care

in matching variables between the models (table 1). Similar to model 1, significant linear trends in mortality were seen with severity of hypoxaemia (mild 28.9% vs 19.3%; moderate 32.8% vs 28.5%; severe 44.5% vs 22.0%; $\chi^2=58.3; p<0.001$), and with increase in the number of quadrants in patients with ARDS compared with AHRF controls, the absolute differences were lower compared with model 1 (mild 28.9% vs 19.3%; moderate 32.8% vs 28.5%; severe 44.5% vs 22.0%; $\chi^2=51.5; p<0.001$). The ICU mortality was higher for hyperinflammatory (50.6% vs 26.8%) and hypoinflammatory (28.2% vs 23.2%) ARDS subphenotypes, compared with matched non-AHRF controls ($\chi^2=147.27; p<0.001$).

Range of AFARDS and categories using model 1 and model 2
The AFARDS ranges between 38.0% (95% CI 34.4% to 41.6%) from model 1 (figure 2A) and 20.9% (95% CI 10.5 to 31.4%) from model 2 (figure 2B).

AFARDS varies by severity of hypoxaemia
In model 1, AFARDS increased with worsening severity of hypoxaemia (mild=32.1% (95% CI 24.4% to 39.8%), moderate=36.7% (95% CI 29.4% to 44.1%), severe=49.7% (95% CI 43.4 to 55.9%)) (figure 2A).

Model 2 also highlighted increase in AFARDS with worsening severity of hypoxaemia (mild=25.7% (95% CI 6.1% to 45.3%), moderate=6.1% (95% CI –11.6% to 23.8%) and severe=41.1% (95% CI 25.2% to 57.1%) (figure 2B)).

AFARDS varies by number of quadrants involved on chest radiography
In model 1, AFARDS increased with number of quadrants involved on chest radiography (two=29.4% (95% CI 22.7% to 36.2%), three=38.1% (95% CI 30.8% to 45.4%), four=45.9% (95% CI 40.7% to 51.2%)) (figure 2A).

Model 2 also highlighted increase in AFARDS with number of quadrants involved on chest radiography (two=14.4% (95% CI –3.9% to 32.6%), three=17.9% (95% CI –4.2% to 40.0%), four=28.9% (95% CI 13.4% to 44.3%) (figure 2B)).

AFARDS was higher in hyperinflammatory subphenotype
In model 1, AFARDS was higher in hyperinflammatory subphenotype (hyperinflammatory=58.7% (95% CI 53.3% to 64.1%) vs hypoinflammatory=28.0% (95% CI 23.1% to 33.0%)) (figure 2A).

Model 2 also highlighted higher AFARDS hyperinflammatory subphenotype (hyperinflammatory=28.6% (95% CI 6.9% to 46.7%) vs hypoinflammatory 17.4% (95% CI 4.5% to 30.2%)) (figure 2B).
Critical Care

Model 3 scenario estimating AF_{AHRF}

Model 3 scenario compared 3504 patients with AHRF matched to 7008 non-AHRF controls. Patients with AHRF had higher ICU mortality compared with non-AHRF controls (31.7% vs 14.1%).

The estimated AF_{AHRF} from model 3 was 33.8% (95% CI 30.5% to 37.1%), which is lower than the AF_{ARDS} from model 1 and higher than the AF_{ARDS} from model 2. These differences were reflected in the severity of hypoxaemia and radiography categories (figure 3A).

Model 4 scenario estimating AF_{AHRF-UL}

Model 4 scenario compared 851 patients with AHRF-UL matched to 1702 non-AHRF controls. Patients with AHRF-UL had higher ICU mortality (24.2% vs 14.5%). The estimate of AF_{AHRF-UL} was 21.3% (95% CI 12.8% to 29.7%), which was lower than the AF_{ARDS} from model 1 and model 2 (figure 3B).

In patients with unilateral, two-quadrant involvement, who would be excluded from ARDS RCTs, the estimate of AF_{AHRF-UL} was 22.8% (95% CI 7.0% to 38.7%), which was comparable to AF_{ARDS} from model 2.

Sample size requirements for ARDS RCTs change with estimated AF_{ARDS}

As the AF_{ARDS} increases in a RCT population, the sample size required will decrease for prespecified alpha, beta and risk reduction combinations. For example, from our current work, sample size estimates were lower for severe hypoxaemia compared with mild or moderate hypoxaemia, and lower for four quadrant radiographic involvement, compared with two or three quadrant radiographic involvement, and lower for hyperinflammatory subphenotype, compared with hypoinflammatory subphenotype (figure 4).

Sensitivity analyses

Overall unmatched estimates of AF_{ARDS}, AF_{AHRF} and AF_{AHRF-UL} were consistent with overall estimates from matched analyses. In the unmatched analyses of model 1, model 3 and model 4—which led to an increase in number of controls—trends within enrichment categories were no longer significant. In the unmatched analysis of model 2—which led to an increase in number of exposed patients with ARDS—trends within enrichment categories were consistent with the matched analysis (table 2).

Overall estimate of AF_{ARDS} in model 2 was lower when hospital mortality was used as the outcome measure instead of ICU mortality; subpopulation estimates were also consistently lower, but overall trends within enrichment categories remained consistent (table 2).

DISCUSSION

Using the LUNG-SAFE database, we report mean estimates of AF_{ARDS} between 20.9% and 38.0%. We observed a dose-response increase in AF_{ARDS} with severity of hypoxaemia and with quadrants of radiographic involvement. AF_{ARDS} was higher in the hyperinflammatory compared with the hypoinflammatory subphenotype of ARDS. Our results are consistent with previous work on AF_{ARDS}17 18 and we have extended these previous works by modelling distinct clinical scenarios, including the value of incorporating patients with AHRF in the extended ARDS case definitions.17 Of note, our AF_{ARDS} estimates are consistent with a very different approach using marginal structural models, reported by Torres et al.17

We focused on several a priori defined ARDS subpopulations that have the potential for enrichment in clinical trials.53 From our previous work, higher all-cause control-arm mortality does not necessarily generate larger average treatment effects in ARDS RCTs,12 making us hypothesise that ARDS-specific enrichment

Figure 4  Illustrative examples of sample size calculations for different AF_{ARDS} scenarios. These curves illustrate the AF_{ARDS} principle. Each curve represents the sample sizes required for different AF estimates (when control event rate is fixed at 40%). We show the estimates of AF_{ARDS} from model 1, stratified by (A) severity of hypoxaemia, (B) maximum number of quadrants involved on chest radiography at 48 hours and (C) subphenotype of ARDS. We contrast these against the common assumption that AF_{ARDS} is expected to be 100%. Dot plots represent ARDS RCTs with mortality as primary outcome identified previously in our systematic review,12; they correspond to the actual RRR used for sample size estimation and sample size per group in these RCTs. Median (IQR) control group mortality used for sample size calculations in these RCTs was 45.0% (33.3%–52.5%) and RRR was 29.0% (24.5%–33.3%). Most trials aimed for 80% power and 5% alpha. The sample size per group varied between 53 and 704 patients. RCTs above a curve will have an adequate sample size to detect the predicted RRR. AF, attributable fraction; ARDS, acute respiratory distress syndrome; RCT, randomised controlled trial; RRR, relative risk reduction.


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subgroups may outperform generic illness severity-based prognostic enrichment.

Enrichment strategy, whether prognostic or predictive, is a trade-off between population prevalence, feasibility and expected treatment effect.\textsuperscript{54} In the LUNG-SAFE cohort, 23.6\% of patients had severe ARDS, 36.7\% had four-quadrant involvement and 36.4\% were hyperinflammatory ARDS subphenotype. Severe hypoxaemia is a potentially implementable enrichment strategy for ARDS RCTs, by using the approach highlighted within the Kigali modification of the ARDS definitions.\textsuperscript{55,56} Furthermore, in previous RCTs of prone positioning and extracorporeal support,\textsuperscript{25,30,37} enriching on severe hypoxaemia has shown promise. Another element of the AHRF-ARDS debate is the interobserver and intraobserver reliability of chest radiology, and its feasibility in resource-limited settings. While acknowledging this debate,\textsuperscript{38} four-quadrant involvement appears to be an enrichment marker for high AFARDS. Another enrichment strategy linked to precision medicine is the subphenotyping of ARDS, which would require either measuring discriminant biomarkers with near patient testing, or implementing a machine learning-derived classifier models incorporating clinically available data. Similar subphenotypic have been reported in non-ARDS populations including COVID-19,\textsuperscript{2} AHRF and sepsis, which potentially broadens the implications of our findings.\textsuperscript{59} For illustration, we compared the sample size estimations from 28 ARDS RCTs\textsuperscript{22–49} that used mortality as a primary outcome, for different AFARDS scenarios (figure 4), which suggests that previous ARDS RCTs may lack sensitivity under the key assumption that only AFARDS deaths are affected by the tested treatment.

Our findings also lead us to consider how our work informs the debate on the need for distinction between ARDS and AHRF. Specifically, the estimate of AFARDS for patients with unilateral, two-quadrant involvement, who would be excluded currently from ARDS RCTs, was comparable to AFARDS from model 2. Currently, ARDS is conceptualised as a subset of AHRF; exclusion of patients with AHRF with similar AF and overlapping biology\textsuperscript{60} from the overall definition has implications for future RCTs and generalisability to clinical practice. Future research should explore the impact of including these populations in ARDS/AHRF RCTs.

Our analysis has strengths and limitations. We used the LUNG-SAFE dataset—a large multinational cohort recruited from 459 ICUs that was prospectively designed to enrol and follow-up patients with AHRF and which underwent systematic validation after data collection. Our assessment of enrichment categories used inclusion criteria that would be immediately applicable to inform design of ARDS RCTs. Despite the use of propensity score methods, residual confounding remains a concern, given the available characteristics of controls and because we have not accounted for differences in mortality between study site and countries. Although we have not accounted for risk factors for ARDS, type of comorbidity, potential worsening (or improvement) over time in hypoxaemia and geographic variations in usual care/outcomes in these analyses, eligibility criteria in ARDS RCTs seldom stipulate these covariates.\textsuperscript{3} The risk factor of

### Table 2  Sensitivity analysis—overall and subpopulation estimates of AFARDS, AF AHRF, and AF AHRF-UL

<table>
<thead>
<tr>
<th>Sensitivity analysis</th>
<th>Model 1: AFARDS (non-AHRF controls)</th>
<th>Matched analysis—hospital mortality as outcome</th>
<th>Model 3: AF AHRF (non-AHRF controls)</th>
<th>Model 4: AF AHRF-UL (non-AHRF controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ARDS/AHRF</td>
<td>2653</td>
<td>851</td>
<td>3504</td>
<td>8407</td>
</tr>
<tr>
<td>Controls</td>
<td>8407</td>
<td>851</td>
<td>8407</td>
<td>8407</td>
</tr>
<tr>
<td>Overall AF</td>
<td>25.2% (22.7%–27.6%)</td>
<td>22.3% (14.4%–30.1%)</td>
<td>17.7% (7.7%–27.6%)</td>
<td>26.5% (23.9%–29.1%) 5.9% (4.1%–7.7%)</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio (mm Hg)</td>
<td>&gt;200 8.9% (4.5%–13.4%)</td>
<td>10.7% (−1.6%–23.0%)</td>
<td>25.8% (7.6%–43.9%)</td>
<td>10.6% (6.3%–15.0%) 2.5% (−2.5%–7.5%)</td>
</tr>
<tr>
<td></td>
<td>100–200 17.2% (13.4%–21.1%)</td>
<td>23.6% (13.2%–34.0%)</td>
<td>3.1% (−13.7%–19.9%)</td>
<td>18.9% (15.2%–22.7%) 3.6% (1.3%–8.5%)</td>
</tr>
<tr>
<td></td>
<td>&lt;100 14.5% (10.7%–18.5%)</td>
<td>33.9% (25.9%–41.9%)</td>
<td>35.0% (18.9%–51.2%)</td>
<td>15.6% (11.7%–19.5%) 1.6% (−3.5%–6.7%)</td>
</tr>
<tr>
<td>Maximum number of quadrants involved in first 48 hours</td>
<td>One – – – 3.9% (−1.0%–8.8%)</td>
<td>2.7% (−1.0%–8.8%)</td>
<td>– – – 3.9% (−1.0%–8.8%)</td>
<td>– – – 2.7% (−1.0%–8.8%)</td>
</tr>
<tr>
<td></td>
<td>Two 11.3% (7.0%–15.6%)</td>
<td>9.7% (−2.9%–22.4%)</td>
<td>12.0% (−5.3%–29.4%)</td>
<td>12.8% (8.6%–17.0%) 2.3% (−2.7%–7.3%)</td>
</tr>
<tr>
<td></td>
<td>Three 10.8% (6.6%–15.1%)</td>
<td>20.0% (9.7%–30.2%)</td>
<td>18.3% (−1.8%–38.5%)</td>
<td>10.9% (6.6%–15.1%) –</td>
</tr>
<tr>
<td></td>
<td>Four 18.8% (15.1%–22.4%)</td>
<td>36.4% (28.2%–44.6%)</td>
<td>22.3% (7.0%–37.6%)</td>
<td>18.7% (15.1%–22.4%) –</td>
</tr>
<tr>
<td>Subphenotype</td>
<td>Hypoinflammatory 18.3% (14.4%–22.1%)</td>
<td>21.3% (10.2%–32.4%)</td>
<td>14.1% (1.9%–26.3%)</td>
<td>– –</td>
</tr>
<tr>
<td></td>
<td>Hyperinflammatory 19.4% (15.9%–23.0%)</td>
<td>31.9% (22.4%–41.5%)</td>
<td>25.9% (7.4%–44.4%)</td>
<td>– –</td>
</tr>
</tbody>
</table>
ARDS limitation is explicit, as the LUNG-SAFE cohort did not collect ARDS risk factors for non-ARDS controls. Our primary and sensitivity analyses focus on mortality; the impact on other outcomes used in ARDS RCTs (such as ventilator-free days) needs to be assessed. An implicit assumption in these models is that the putative treatment for ARDS/AHRF has no effect on mortality of patients with non-ARDS/non-ARDH. This assumption would not bias AF-ARDS estimates, as the control groups needs to be assessed. An implicit assumption in these models has higher attributable fraction.

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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, almitrine 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/µL), 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.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographical region</td>
<td>Prospective cohort study; EARLI and VALID studies</td>
<td>Prospective cohort study</td>
<td>Prospective cohort study; LUNG-SAFE</td>
</tr>
<tr>
<td>Selected cohort</td>
<td>Mechanically ventilated patients with sepsis</td>
<td>ICU patients with sepsis</td>
<td>Mechanically ventilated patients</td>
</tr>
<tr>
<td>Patients with ARDS (n)</td>
<td>EARLI; 195 VALID; 99</td>
<td>141</td>
<td>Model-1; 2653 Model-2; 851</td>
</tr>
<tr>
<td>Statistical method to estimate AF</td>
<td>Logistic regression</td>
<td>Survival analysis with targeted minimum loss-based estimation</td>
<td>Logistic regression (in propensity score matched population)</td>
</tr>
<tr>
<td>Variables adjusted</td>
<td>Age, sex, race, chronic comorbidities, illness severity (SAPS II/APACHE II/APACHE III), acute comorbidities (shock/pneumonia)</td>
<td>Age, sex, chronic comorbidities, illness severity, invasive mechanical ventilation</td>
<td>Age, sex, chronic comorbidities, illness severity (non-pulmonary SOFA), invasive mechanical ventilation</td>
</tr>
<tr>
<td>AF estimate (95% CI)</td>
<td>EARLI; 27% (14 - 37%) VALID; 37% (10 - 51%)</td>
<td>15% (3 - 26%)</td>
<td>Model-1; 38% (34 - 42%) Model-2; 21% (11 - 31%)</td>
</tr>
</tbody>
</table>

**eTable-1 Comparison of studies estimating AF<sub>ARDS</sub>**

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.
### 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<sub>2</sub>: inspired fraction of oxygen; ICU: intensive care unit; LOS: length of stay; PaO<sub>2</sub>: arterial oxygen tension; SOFA: sequential organ failure assessment

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARDS</th>
<th>AHRF-UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;:FiO&lt;sub&gt;2&lt;/sub&gt; ratio on day 1</td>
<td>1 (0.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Maximum number of quadrants involved in first 48 hours</td>
<td>-</td>
<td>17 (2.0)</td>
</tr>
<tr>
<td>Sub-phenotype</td>
<td>-</td>
<td>851 (100.0)</td>
</tr>
<tr>
<td>Non respiratory SOFA score day 1</td>
<td>5 (0.2)</td>
<td>-</td>
</tr>
<tr>
<td>Duration of invasive mechanical ventilation</td>
<td>400 (15.1)</td>
<td>150 (17.6)-</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>57 (2.1)</td>
<td>21 (2.5)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>10 (0.4)</td>
<td>4 (0.5)</td>
</tr>
</tbody>
</table>

### eTable-2b. Variables reported for non-AHRF controls

AHRF: acute hypoxaemic respiratory failure; ICU: intensive care unit; LOS: length of stay; SD: standard deviation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-AHRF controls (N = 8407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (SD)</td>
<td>61.1 (17.2)</td>
</tr>
<tr>
<td>Sex Female n (%)</td>
<td>3434 (40.8)</td>
</tr>
<tr>
<td>ICU LOS Mean (SD)</td>
<td>6.2 (8.0)</td>
</tr>
<tr>
<td>ICU mortality n (%)</td>
<td>1194 (14.0)</td>
</tr>
</tbody>
</table>
### eTable-3a. Relationship between severity of hypoxaemia and chest radiograph findings in LUNGSAFE cohort.

<table>
<thead>
<tr>
<th>Severity of hypoxaemia; ( \text{PaO}_2: \text{FiO}_2 ) (mmHg)</th>
<th>Maximum number of quadrants involved on chest radiograph in first 48 hours</th>
<th>Two n (%)</th>
<th>Three n (%)</th>
<th>Four n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild; &gt; 200</td>
<td></td>
<td>394 (51.8)</td>
<td>158 (20.8)</td>
<td>208 (27.4)</td>
</tr>
<tr>
<td>Moderate; 100 – 200</td>
<td></td>
<td>499 (39.5)</td>
<td>318 (25.2)</td>
<td>446 (35.3)</td>
</tr>
<tr>
<td>Severe; &lt; 100</td>
<td></td>
<td>151 (24.1)</td>
<td>139 (22.2)</td>
<td>336 (53.7)</td>
</tr>
</tbody>
</table>

### eTable-3b. Relationship between severity of hypoxaemia and ARDS sub-phenotype in LUNGSAFE cohort

<table>
<thead>
<tr>
<th>Severity of hypoxaemia; ( \text{PaO}_2: \text{FiO}_2 ) (mmHg)</th>
<th>ARDS sub-phenotype</th>
<th>Hypoinflammatory n (%)</th>
<th>Hyperinflammatory n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild; &gt; 200</td>
<td></td>
<td>581 (76.4)</td>
<td>179 (23.6)</td>
</tr>
<tr>
<td>Moderate; 100 – 200</td>
<td></td>
<td>929 (73.6)</td>
<td>334 (26.4)</td>
</tr>
<tr>
<td>Severe; &lt; 100</td>
<td></td>
<td>452 (72.2)</td>
<td>174 (27.8)</td>
</tr>
</tbody>
</table>

ARDS: acute respiratory distress syndrome
Table 1: Matching variables for propensity models used to estimate attributable fraction

<table>
<thead>
<tr>
<th></th>
<th>Model-1 AFARDS</th>
<th>Model-2 AFARDS</th>
<th>Model-3 AFARHF</th>
<th>Model-4 AFARHF-UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARDS (N=2653)</td>
<td>Non-AHRF (N=5306)</td>
<td>AHRF-UL (N=851)</td>
<td>AHRF-UL (N=851)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years) Mean (SD)</strong></td>
<td>61.5 (16.8)</td>
<td>61.4 (16.8)</td>
<td>63.0 (16.2)</td>
<td>63.0 (16.9)</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td><strong>Sex Female n (%)</strong></td>
<td>1014 (38.2)</td>
<td>2028 (38.2)</td>
<td>297 (34.9)</td>
<td>301 (35.4)</td>
</tr>
<tr>
<td></td>
<td>0.00</td>
<td>0.01</td>
<td>-0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Number of comorbidities n (%)</strong></td>
<td>NMV</td>
<td>NMV</td>
<td>NMV</td>
<td>NMV</td>
</tr>
<tr>
<td>0</td>
<td>330 (38.8)</td>
<td>322 (37.8)</td>
<td>NMV</td>
<td>NMV</td>
</tr>
<tr>
<td>1</td>
<td>302 (35.5)</td>
<td>302 (35.5)</td>
<td>NMV</td>
<td>NMV</td>
</tr>
<tr>
<td>2 or more</td>
<td>219 (25.7)</td>
<td>227 (26.7)</td>
<td>-0.02</td>
<td>NMV</td>
</tr>
<tr>
<td>Ventilated on day 1 n (%)</td>
<td>700 (82.3)</td>
<td>698 (82.0)</td>
<td>0.01</td>
<td>NMV</td>
</tr>
</tbody>
</table>

eTable-4 Matching variables for propensity models used to estimate attributable fraction

AFARDS 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. AFARDS 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. AFARHF in Model-3 was estimated by matching 3504 ARHF cases to non-AHRF controls that were propensity score balanced on age and sex in a 1:2 ratio. AFARHF-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: \( AF_{\text{ARDS}} \) estimate

- Age
- Sex

ARDS → Death

Matched to ICU controls receiving mechanical ventilation without AHRF

Model 2: \( AF_{\text{ARDS}} \) estimate

- Age
- Sex
- Comorbidity

ARDS → Illness severity → Death

Matched to ICU controls receiving mechanical ventilation with AHRF with unilateral infiltrates only
Model 3: $AF_{AHRF}$ estimate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Confounder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AHRF $\rightarrow$ Death

Matched to ICU controls receiving mechanical ventilation without AHRF

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Confounder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AHRF-UL $\rightarrow$ Death

Matched to ICU controls receiving mechanical ventilation without AHRF

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

Age

Sex - Female

Sex - Male

Empirical cumulative density

Proportion

0.0 0.2 0.4 0.6 0.8 1.0

0.0 0.2 0.4 0.6 0.8 1.0

0.0 0.2 0.4 0.6 0.8 1.0

0.0 0.2 0.4 0.6 0.8 1.0

0.0 0.2 0.4 0.6 0.8 1.0

0.0 0.2 0.4 0.6 0.8 1.0

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