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

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Contributorship

RS, DM, and MS-H were responsible for study concept and design. RS, TP, PS, MM, GB, JL and MS-H had full access to all the data in the study and take responsibility for the integrity and accuracy of the data analyses. RS, TP, PS, MM, GB, EF, CS, AD, GR, CC, JL, DM, MS-H contributed to data interpretation. RS and MS-H undertook the statistical analyses. RS and MS-H drafted the manuscript; RS, TP, PS, MM, GB, EF, CS, AD, GR, CC, JL, DM, MS-H contributed to critical revision of the manuscript for important intellectual content. MS-H was responsible for overall supervision. Funding for the LUNG-SAFE study was obtained by GB and JL.

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Ethics approval

All participating ICUs individually obtained local ethics committee approval and obtained either patient consent or ethics committee waiver of consent in the original LUNG SAFE study. Research ethics board approval - St. Michael's Hospital (one of two lead sites) REB# 13–384.

Data sharing

Requests for access to the LUNG-SAFE dataset should be submitted to research@esicm.org

Disclaimer

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Abstract

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

Methods: We performed a matched case-control study using the LUNG-SAFE 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 AF_{ARDS} 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 AF_{ARDS} in subgroups based on severity of hypoxaemia, number of lung quadrants involved, and hyper- versus hypo-inflammatory phenotypes. Additionally, we derived AF_{AHRF} estimates by matching patients with AHRF to non-AHRF controls, and $AF_{AHRF\text{-}UL}$ estimates by matching patients with AHRF-UL to non-AHRF controls.

Results: Estimated AF_{ARDS} was 20.9%(95%CI 10.5–31.4%) when compared to AHRF -UL controls and 38.0%(95%CI 34.4%−41.6%) compared to non-AHRF controls. Within subgroups, estimates for AF_{ARDS} compared to AHRF-UL controls were highest in patients with severe hypoxaemia (41.1%(95%CI 25.2–57.1%)), in those with four quadrant involvement on chest radiography (28.9%(95%CI 13.4–44.3%)), and in the hyperinflammatory sub-phenotype (26.8%(95%CI 6.9–46.7%)). Estimated AF_{AHRF} was 33.8%(95%CI 30.5%−37.1%) compared to non-AHRF controls. Estimated $AF_{AHRF\text{-}UL}$ was 21.3%(12.8–29.7%) compared to non-AHRF controls

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

Keywords

Acute Respiratory distress syndrome; Attributable fraction; randomised clinical trials

Introduction

Acute respiratory distress syndrome (ARDS) refers to acute hypoxaemic respiratory failure (AHRF) occurring within one 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 plausibility[2] and strong supporting pre-clinical evidence, when tested within randomised clinical trials (RCTs)[3], often report statistically indeterminate results (i.e., 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 sub-phenotypes of ARDS respond differentially to treatments[5–11]. *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[12].

In this manuscript, we explore another explanation – variation in the excess fraction of mortality attributable to ARDS (AF_{ARDS})[13, 14] in RCT participants. Patients with ARDS may die *from* ARDS (i.e., AF_{ARDS}) or *with* ARDS (i.e., 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_{ARDS} estimates (I.e., 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_{ARDS} will vary by severity of hypoxaemia as per the Berlin ARDS definitions[1, 15], by number of quadrants affected on chest radiography[16], and by sub-phenotype. Our hypothesis was informed by the following observations: first, two small cohort studies (eTable-1) indicated that AF_{ARDS} ranges between 15% and 37%[17, 18];

second, in the Berlin ARDS definitions, ARDS outcomes worsened with increasing severity of hypoxaemia[1]. Third, the hyperinflammatory ARDS sub-phenotype had higher mortality and greater treatment effect within RCTs [5–11]. Recently, these ARDS sub-phenotypes were identified within the LUNG-SAFE cohort using machine learning models [19], are available as predefined categories within the LUNG-SAFE dataset, and currently there are no AF_{ARDS} estimates for them. Given recent proposals to include AHRF patients (including those with unilateral infiltrates[20]) within an expanded ARDS case definition[21], we also compared AF_{AHRF} and AF_{ARDS}.

Methods

Data source

Our data source was the well described LUNG-SAFE (Large observational study to Understand the Global impact of Severe Acute respiratory FailurE) dataset. We summarise key elements of the LUNG-SAFE study design and data collection in eMethods-1. National coordinators and site investigators of the LUNG-SAFE study are listed in the online supplement. AHRF was defined as concurrent presence of: (a) arterial oxygen tension: inspired fraction of oxygen (PaO_2:FiO_2) ratio ≤ 300 mmHg; (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 ≥ 5 cmH_2O. 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[15].

Study population

Selection criteria of AHRF/ARDS cohort reported in this manuscript were described previously by Pham et al[20]. We defined four populations for our matched cohort study, after excluding patients with congestive heart failure: (1) ARDS – AHRF patients who met the Berlin ARDS criteria, (2) AHRF – patients who met criteria for AHRF (and therefore includes all ARDS patients), (3) AHRF patients with unilateral infiltrates (AHRF-UL) - met 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, ICU length of stay and ICU mortality.

ARDS sub-phenotypes have recently been assigned in the LUNG-SAFE cohort using a clinical classifier model with a limited selection of predictor variables[19] (eMethods-2). Of note, this model used optimised probability cutoffs and did not use latent class analysis to assign sub-phenotypes. Patients without ARDS do not have sub-phenotype allocation There were no patients who had unilateral infiltrates without AHRF, to act as controls for AF_{AHRF} range estimates, similar to the AF_{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[3]. Pre-defined

enrichment categories within the primary exposures were severity of hypoxaemia, number of quadrants affected on chest radiography, and sub-phenotypes. Due to the low proportion of missing data (e-Table 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_{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 sub-phenotype) would also vary based on matching, enabling estimation of variation in AF_{ARDS} within these categories, along with AF_{ARDS} range.

Propensity score models and scenarios

Model-1 scenario: AF_{ARDS} could be reduced with treatment to mortality seen in ICU patients of similar age and sex without AHRF (one ARDS patient was matched to two non-AHRF controls).

Model-2 scenario: AF_{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 ARDS patient was matched to one AHRF-UL control).

Model-3 scenario: AF_{AHRF} could be reduced with treatment to mortality seen in ICU patients of similar age and sex without AHRF (one AHRF patient was matched to two non-AHRF controls)

Model-4 scenario: $AF_{AHRF\text{-}UL}$ could be reduced with treatment to mortality seen in ICU patients of similar age and sex without AHRF scenario (one AHRF-UL patient 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, eMethods-3, and eFigure-1. We used four separate logistic regression models to estimate AF (AF_{ARDS}, AF_{AHRF}, $AF_{AHRF\text{-}UL}$).

Estimation of AF_{ARDS} range

We used model-1, and model-2 to estimate the variation in AF_{ARDS} by severity of hypoxaemia categories (mild (PaO_2:FiO_2 >200mmHg); moderate (PaO_2:FiO_2 100–200mmHg), or severe (PaO_2:FIO_2 <100mmHg)); the number of quadrants involved radiographically in the first 48 hours after ICU admission (two, three, or four), and the hyperinflammatory vs hypoinflammatory ARDS subphenotypes within LUNG-SAFE dataset[19].

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 $AF_{AHRF\text{-}UL}$

We used model-4 to estimate the variation in $AF_{AHRF\text{-}UL}$ 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 AF_{ARDS} based sample size estimates for different enrichment subgroups

To illustrate how AF_{ARDS} can influence sample size estimation, we compared predicted sample size estimates from 28 published ARDS RCTs[22–49] that used mortality as primary outcome (identified in our previous systematic review[3]) to simulated sample size estimates. We simulated sample size calculations for the scenario where AF_{ARDS} = 100%, and for estimates of AF_{ARDS} 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) sub-phenotype 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.

Sensitivity analysis

We report the following sensitivity analyses; (i) unmatched analyses in all 4 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 AF_{ARDS}.

χ^2 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 less than 0.05 were considered statistically significant. All analyses were performed using R version 3.4.2 (AF[50], Matchit[51], and tidyverse[52] packages).

Results

Among 12906 admissions who received ventilatory support in the ICU, we identified 3504 eligible AHRF patients; 2653 met the Berlin ARDS criteria, and 851 patients had AHRF-UL (Figure-1). Missing data are summarised in eTable-2a. Baseline characteristics and outcomes for non-AHRF patients are summarised in eTable-2b. Patients with mild hypoxaemia most often had two quadrant infiltrates, whilst patients with severe hypoxaemia had four quadrant infiltrates (eTable-3a). There was no association between severity of hypoxaemia and ARDS subphenotype (eTable-3b).

Model-1 scenario

Model-1 scenario compared 2653 patients with ARDS matched to 5306 non-AHRF controls. Patients with ARDS had higher ICU mortality compared to 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%; X^2 = 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%; X^2 = 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 (X^2 = 413.07; p<0.001).

Model-2 scenario

Model-2 scenario compared 851 patients with ARDS matched to 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 to model-1 reflecting the differences 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%; X^2 = 58.3; p < 0.001), and with increase in the number of quadrants in patients with ARDS compared with AHRF-UL 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%; X^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 (X^2 = 147.27; p<0.001).

Range of AF_{ARDS} and categories using model-1, and model-2—The AF_{ARDS} ranges between 38.0% (95% CI 34.4% - 41.6%) from model-1(Figure-2a) and 20.9% (95% CI 10.5 – 31.4%) from model-2 (Figure-2b).

AF_{ARDS} varies by severity of hypoxaemia—In model-1, AF_{ARDS} increased with worsening severity of hypoxaemia (mild = 32.1% (95 % CI 24.4 – 39.8%), moderate = 36.7% (95% CI 29.4 – 44.1%), severe = 49.7% (95% CI 43.4 – 55.9%)) (Figure-2a).

Model-2 also highlighted increase in AF_{ARDS} with worsening severity of hypoxaemia (mild = 25.7% (95 % CI 6.1 – 45.3%), moderate = 6.1% (95% CI −11.6 – 23.8%), and severe = 41.1% (95% CI 25.2 – 57.1%) (Figure-2b)).

AF_{ARDS} varies by number of quadrants involved on chest radiography—In model-1, AF_{ARDS} increased with number of quadrants involved on chest radiography (two = 29.4% (95 % CI 22.7 – 36.2%), three = 38.1% (95% CI 30.8 – 45.4%), four = 45.9% (95% CI 40.7 – 51.2%)) (Figure 2a).

Model-2 also highlighted increase in AF_{ARDS} with number of quadrants involved on chest radiography (two = 14.4% (95 % CI −3.9 – 32.6%), three = 17.9% (95% CI −4.2 – 40.0%), four = 28.9% (95% CI 13.4 – 44.3%) (Figure-2b)).

AF_{ARDS} was higher in hyperinflammatory subphenotype—In model-1, AF_{ARDS} was higher in hyperinflammatory subphenotype (hyperinflammatory= 58.7% (95% CI 53.3 – 64.1%) vs hypoinflammatory = 28.0% (95 % CI 23.1 – 33.0%)) (Figure-2a).

Model-2 also highlighted higher AF_{ARDS} the hyperinflammatory subphenotype ((hyperinflammatory= 28.6% (95% CI 6.9 – 46.7%) vs hypoinflammatory 17.4% (95% CI 4.5 – 30.2%) (Figure-2b).

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% - 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 $AF_{AHRF\text{-}UL}$

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 $AF_{AHRF\text{-}UL}$ was 21.3% (95% CI 12.8% - 29.7%), which was which lower than the AF_{ARDS} from model-1 and comparable to model-2 (Figure-3b). In patients with unilateral, two-quadrant involvement, who would be excluded from ARDS RCTs, the estimate of $AF_{AHRF\text{-}UL}$ was 22.8% (95% CI 7.0% - 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 pre-specified alpha, beta, and risk reduction combinations. For example, from our current work, sample size estimates were lower for severe hypoxaemia compared to mild or moderate hypoxaemia, and lower for four quadrant radiographic involvement, compared with two or three quadrant radiographic involvement, and lower for hyperinflammatory sub-phenotype, compared with hypo-inflammatory sub-phenotype (Figure-4).

Sensitivity analyses—Overall unmatched estimates of AF_{ARDS}, $AF_{AHRF\ and}$ $AF_{AHRF\text{-}UL}$ 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% to 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[21]. Of note, our AF_{ARDS} estimates are consistent with a very different approach using marginal structural models, reported by Torres and colleagues[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 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[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 criteria for ARDS RCTs, by using the approach highlighted within the Kigali modification of the ARDS definitions[55, 56]. Further, in previous RCTs of prone positioning and extracorporeal support[30, 57, 58] enriching on severe hypoxaemia has shown promise. Another element of the AHRF-ARDS debate is the inter- and intra-observer reliability of chest radiology, and its feasibility in resource limited settings. Whilst acknowledging this debate[59], four-quadrant involvement appears to be an enrichment marker for high AF_{ARDS}.

Another enrichment strategy linked to precision medicine is the subphenotyping of ARDS, which would require either measuring discriminant biomarkers with near patient testing, or implementation of machine learning-derived classifier models incorporating clinically available data. Similar subphenoptypes have been reported in non-ARDS populations including COVID-19[6], AHRF and sepsis, which potentially broadens the implications of our findings[60]. For illustration, we compared the sample size estimations from 28 ARDS RCTs[22–49], that used mortality as a primary outcome, for different AF_{ARDS} scenarios (Figure-4), which suggests that previous ARDS RCTs may lack sensitivity under the key assumption that only AF_{ARDS} 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 $AF_{AHRF\text{-}UL}$ for patients with unilateral, two-quadrant involvement, who would be excluded currently from ARDS RCTs, was comparable to AF_{ARDS} from model-2. Currently ARDS is conceptualised as a subset of AHRF; exclusion of AHRF patients with similar AF and overlapping biology[61] 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[3]. The risk factor of ARDS limitation is explicit, as the LUNG-SAFE cohort did not collect ARDS risk factors for non-AHRF 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 non-ARDS/non-AHRF patients' mortality. This assumption would not bias AF-ARDS estimates, as the control groups in ARDS RCTs would either not receive the intervention or those who do, will be analysed as crossovers / intention to treat framework.

Conclusions

ARDS is associated with excess mortality in critically ill patients. Our results highlight generic enrichment populations based on commonly used ARDS RCT eligibility criteria such as severity of hypoxaemia, and number of quadrants involved in chest radiography. We show that hyperinflammatory ARDS sub-phenotype has higher attributable fraction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing Interest

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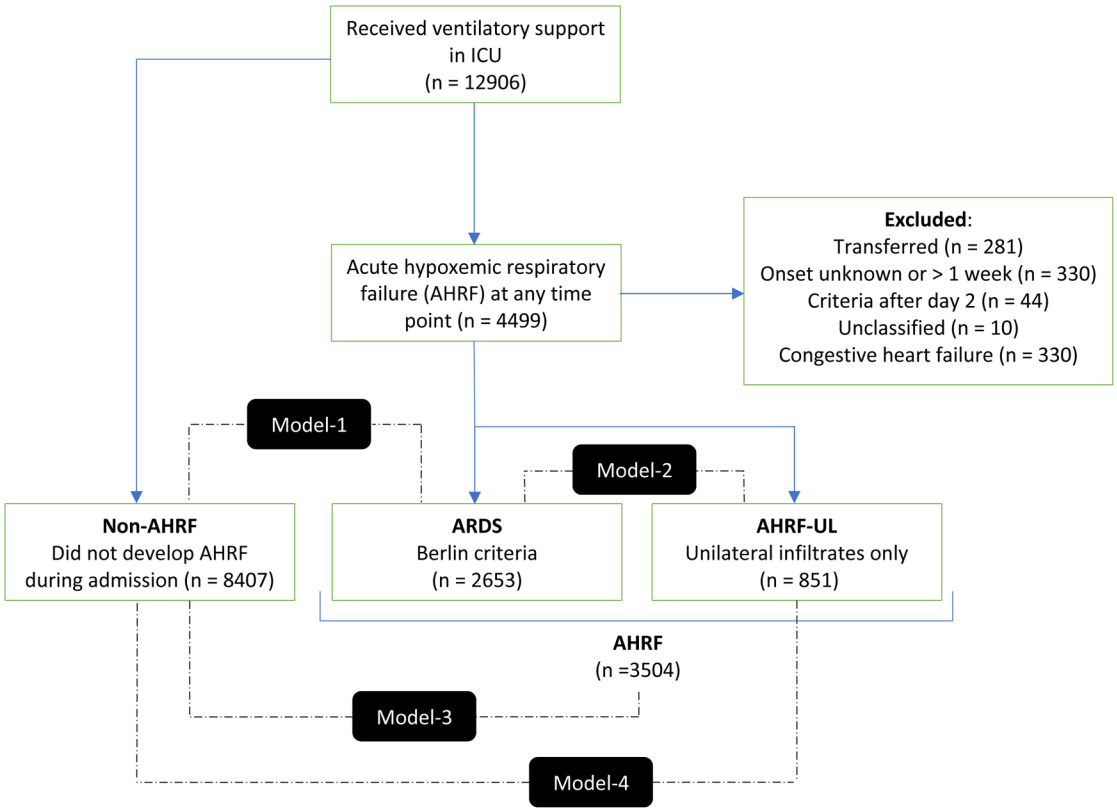
Similar Pattern of Biomarkers of Inflammation and Injury to Acute Respiratory Distress Syndrome Patients. Crit Care Med 2017, 45(11):1845–1853. [PubMed: 28806218]

Key messages

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 15–37%. We do not know how this varies by severity of hypoxaemia, radiographic findings, and ARDS sub-phenotype.

What this study adds: We observed a dose-response increase in AF_{ARDS} with severity of hypoxaemia, quadrants of radiographic involvement, and that AF_{ARDS} was higher in the hyperinflammatory compared with the hypoinflammatory sub-phenotype of ARDS.

How this study might affect research, practice or policy: We highlight ARDS subpopulations that can inform enrichment options in randomised clinical trials.



Model	Propensity model characteristics				AF estimate	Figure
	Exposed n	Controls n	Matching ratio	Matched variables		
1	ARDS 2653	Non-AHRF 5306	1:2	Age, Sex	Overall AF_{ARDS} Subpopulation AF_{ARDS}	2a
2	ARDS 851	AHRF-UL 851	1:1	Age, Sex, Number of comorbidities, Ventilated on Day 1	Overall AF_{ARDS} * Subpopulation AF_{ARDS}	2b
3	AHRF 3504	Non-AHRF 7008	1:2	Age, Sex	Overall AF_{AHRF} Subpopulation AF_{AHRF}	3a
4	AHRF-UL 851	Non-AHRF 1702	1:2	Age, Sex	Overall $AF_{AHRF-UL}$ Subpopulation $AF_{AHRF-UL}$	3b

*Non-respiratory SOFA score (as a marker of illness severity) was included as a covariate in the logistic regression model used to estimate AF_{ARDS} from propensity model-2

Figure-1. Flowchart of patients screened and included in the models used to generate overall and subpopulation estimates of AF_{ARDS}, AF_{AHRF} and $AF_{AHRF-UL}$

AF is the proportion of individuals with the outcome of interest e.g. death that can be attributed to the exposure e.g. ARDS. For example, AF_{ARDS}= [(Deaths in ARDS – Deaths in non-ARDS)/Deaths in ARDS].

Comparisons used to generate overall estimates for AF_{ARDS}, AF_{AHRF}, and $AF_{AHRF-UL}$ are shown in the black rectangles. Further details on each model, and the AF estimates generated are provided in the table. To generate subpopulation estimates, analysis was stratified by severity of hypoxaemia, maximum number of quadrants involved in the first 48 hours, and ARDS sub-phenotype.

ARDS: acute respiratory distress syndrome; AF: attributable fraction; AHRF: acute hypoxaemic respiratory failure; AHRF-UL: acute hypoxaemic respiratory failure with unilateral infiltrates only

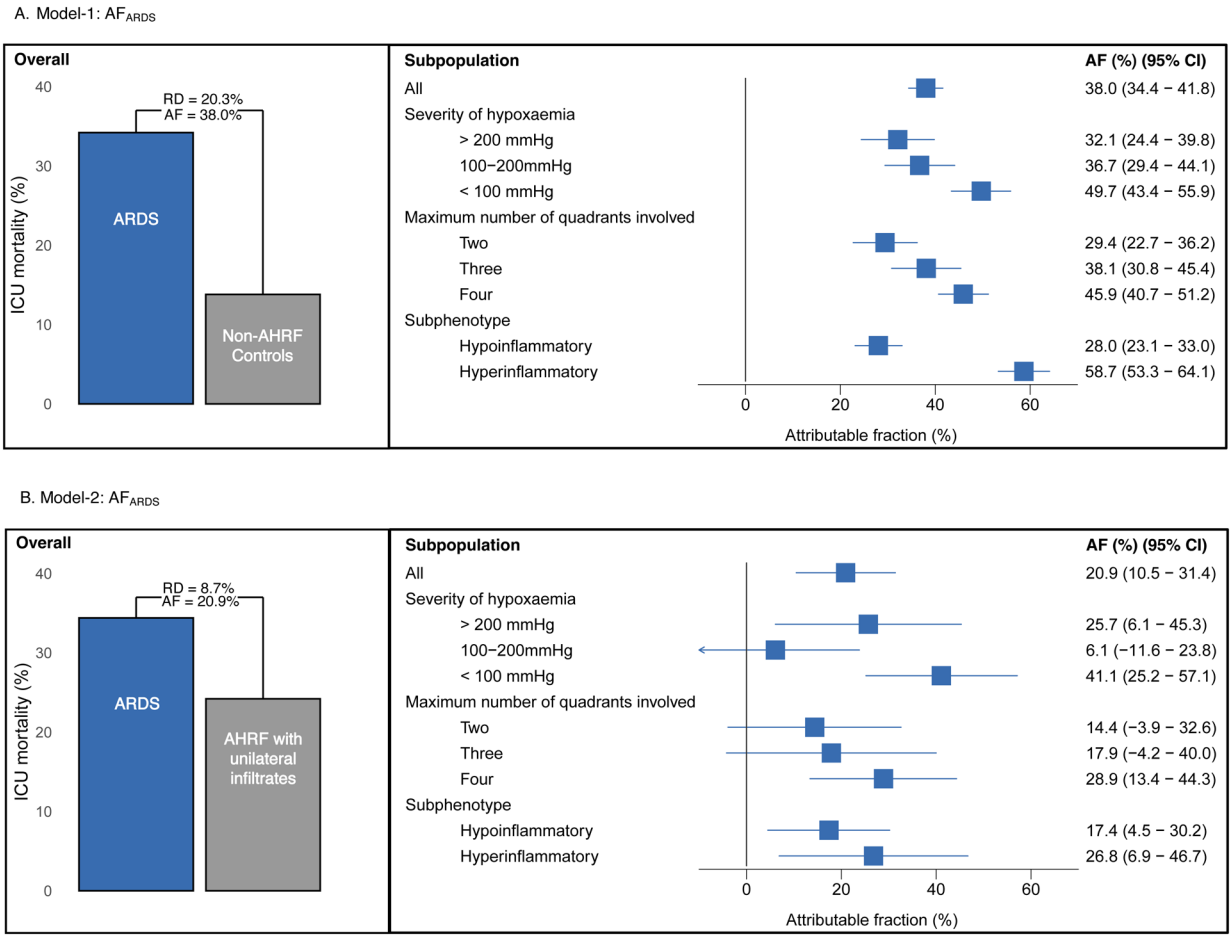


Figure-2. Overall and subpopulation estimates of AF_{ARDS}

Figure-2a. The fraction of deaths attributable to the ARDS exposure was ascertained using proportions. Propensity for ARDS logistic regression models were used to derive estimates for AF_{ARDS} in model-1. Bar graph shows the mortality difference between ARDS population compared with propensity matched non-AHRF controls (Model-1). Analysis was then stratified by severity of hypoxemia, maximum number of quadrants involved in the first 48 hours, and ARDS hypo/hyper-inflammatory subphenotype. Subpopulation AF ARDS estimates from model-1 are shown in the forest plot.

Figure-2b. Propensity for ARDS logistic regression models were then used to derive estimates for AF_{ARDS} in model-2. Bar graph shows the mortality difference between ARDS population compared with propensity matched controls who had AHRF with unilateral infiltrates (Model-2). Analysis was also stratified by severity of hypoxaemia, maximum number of quadrants involved in the first 48 hours, and ARDS hypo/hyper-inflammatory subphenotype. Subpopulation AF_{ARDS} estimates from model-2 are shown in the forest plot. AF: attributable fraction; ARDS: acute respiratory distress syndrome; AHRF: acute hypoxemic respiratory failure; CI: confidence interval; RD: risk difference.

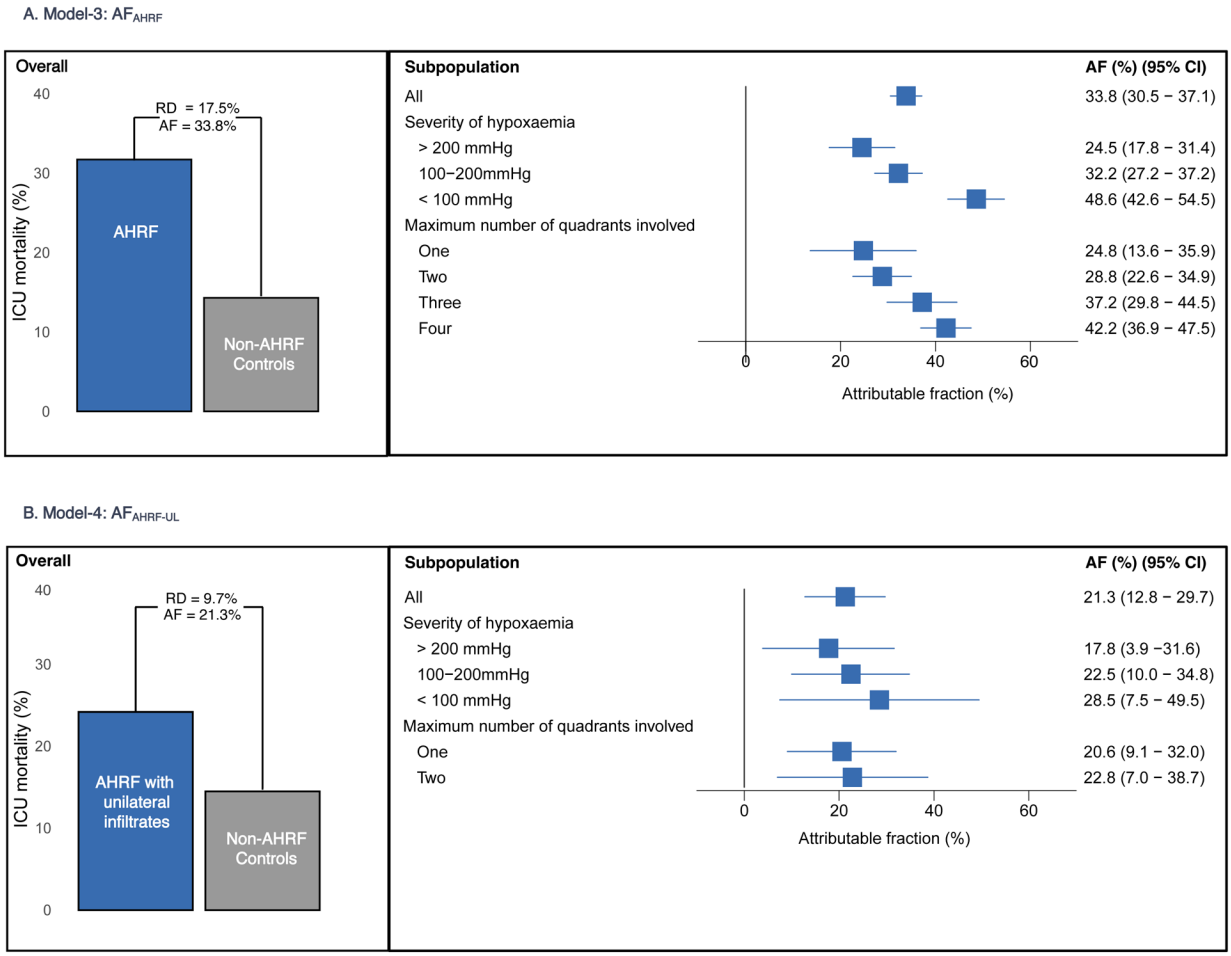


Figure-3. Overall and subpopulation estimates of AF_{AHRF} and $AF_{AHRF\text{-}UL}$

Figure-3a. Bar graphs show the mortality difference between AHRF population compared with propensity matched non-AHRF controls. AF_{AHRF} estimates stratified by severity of hypoxaemia and maximum number of quadrants involved in the first 48 hours are shown in the forest plot.

Figure-3b. Bar graphs show the mortality difference between AHRF-UL population compared with propensity matched non-AHRF controls. $AF_{AHRF\text{-}UL}$ estimates stratified by severity of hypoxemia and maximum number of quadrants involved in the first 48 hours are shown in the forest plot.

AF: attributable fraction; AHRF: acute hypoxemic respiratory failure; AHRF-UL: acute hypoxemic respiratory failure with unilateral infiltrates only; CI: confidence interval; RD: risk difference.

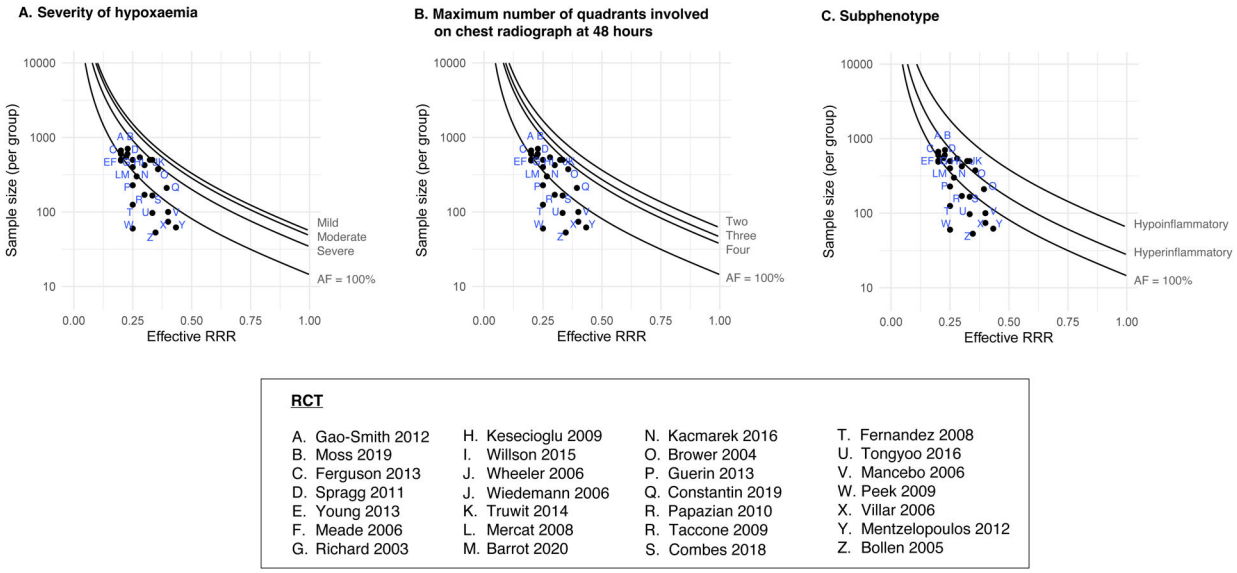


Figure-4. Illustrative examples of sample size calculations for different AF_{ARDS} scenarios

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) sub-phenotype 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 to 704 patients.

RCTs above a curve will have an adequate sample size to detect the predicted RRR.

RRR; relative risk reduction, AF; attributable fraction, ARDS: acute respiratory distress syndrome.

Table 1

Baseline characteristics of ARDS, AHRF, AHRF-UL and corresponding propensity matched control populations to derive ARDS/AHRF attributable fraction.

	Model-1 AF_{ARDS}		Model-2 AF_{ARDS}		Model-3 AF_{AHRF}		Model-4 $AF_{AHRF-UL}$	
	ARDS (N = 2653)	**Non-AHRF (N = 5306)**	**ARDS (N = 851)**	**AHRF-UL (N = 851)**	**AHRF (N = 3504)**	**Non-AHRF (N = 7008)**	**AHRF-UL (N = 851)**	**Non-AHRF (N = 1702)**
Age (years) Mean (SD)	61.5 (16.8)	61.4 (16.8)	63.0 (16.2)	63.0 (16.9)	61.8 (16.8)	62.0 (16.8)	63.0 (16.9)	63.0 (16.8)
Sex Female n (%)	1014 (38.2)	2028 (38.2)	297 (34.9)	301 (35.4)	1315 (37.5)	2664 (38.0)	301 (35.4)	599 (35.2)
BMI Mean (SD)	27.4 (8.6)	-	26.9 (7.3)	26.7 (6.8)	27.3 (8.2)	-	26.7 (6.8)	-
Number of comorbidities n (%)								
0	1053 (39.7)	-	330 (38.8)	322 (37.8)	1375 (39.2)	-	322 (37.8)	-
1	937 (35.3)	-	302 (35.5)	302 (35.5)	1239 (35.4)	-	302 (35.5)	-
2 or more	663 (25.0)	-	219 (25.7)	227 (26.7)	890 (25.4)	-	227 (26.7)	-
Risk factor for ARDS n (%)								
Pneumonia	1574 (59.3)	-	510 (59.9)	433 (50.9)	2007 (57.3)	-	433 (50.9)	-
Extrapulmonary sepsis	421 (15.9)	-	141 (16.6)	115 (13.5)	536 (15.3)	-	115 (13.5)	-
Aspiration	386 (14.5)	-	114 (13.4)	157 (18.4)	543 (15.5)	-	157 (18.4)	-
Pancreatitis	57 (2.1)	-	16 (1.9)	11 (1.3)	68 (1.9)	-	11 (13)	-
Pulmonary vasculitis	12 (0.5)	-	2 (0.2)	0 (0)	12 (0.3)	-	0 (0.0)	-
Trauma	108 (4.1)	-	37 (4.3)	48 (5.6)	156 (4.5)	-	48 (5.6)	-
Inhalation	69 (2.6)	-	28 (3.3)	22 (2.6)	91 (2.6)	-	22 (2.6)	-
Pulmonary contusion	82 (3.1)	-	28 (3.3)	34 (4.0)	116 (3.3)	-	34 (4.0)	-
Burns	7 (0.3)	-	3 (0.4)	2 (0.2)	9 (0.3)	-	2 (0.2)	-
Non-cardiogenic shock	201 (7.6)	-	75 (8.8)	52 (6.1)	253 (7.2)	-	52 (6.1)	-
Drowning	2 (0.1)	-	1 (01)	0 (0)	2 (0.1)	-	0 (0.0)	-
Drug overdose	47 (1.8)	-	11 (1.3)	22 (2.6)	69 (2.0)	-	22 (2.6)	-
Transfusion-related	107 (4.0)	-	34 (4.0)	27 (3.2)	134 (3.8)	-	27 (3.2)	-
Other	67 (2.5)	-	17 (2.0)	45 (5.3)	112 (3.2)	-	45 (5.3)	-
No risk factor for ARDS	229 (8.6)	-	79 (9.3)	0 (0)	229 (6.5)	-	0 (0.0)	-
PaO_2:FiO_2 ratio on day 1 Mean (SD) *	159 (67.4)	-	161 (67.6)	188 (63.6)	166 (67.8)	-	188 (63.6)	-
Severity of hypoxemia on day 1 n (%)								
Mild (200–300)	760 (28.6)	-	249 (29.3)	377 (44.3)	1137 (32.4)	-	377 (44.3)	-
Moderate (100–200)	1263 (47.6)	-	400 (47.0)	380 (44.7)	1643 (46.9)	-	380 (44.7)	-

	Model-1 AF_{ARDS}		Model-2 AF_{ARDS}		Model-3 AF_{AHRF}		Model-4 $AF_{AHRF-UL}$	
	ARDS (N = 2653)	**Non-AHRF (N = 5306)**	**ARDS (N = 851)**	**AHRF-UL (N = 851)**	**AHRF (N = 3504)**	**Non-AHRF (N = 7008)**	**AHRF-UL (N = 851)**	**Non-AHRF (N = 1702)**
Severe (<100)	626 (23.6)	-	200 (23.5)	93 (10.9)	719 (20.5)	-	93 (10.9)	-
Maximum number of quadrants involved in first 48 hours n (%) *								
1	-	-	-	598 (70.2)	482 (13.8)	-	482 (70.2)	-
2	1045 (39.4)	-	351 (41.2)	236 (27.7)	1281 (36.6)	-	236 (27.7)	-
3	615 (23.2)	-	214 (25.1)	-	624 (17.8)	-	-	-
4	993 (37.4)	-	286 (33.6)	-	1000 (28.5)	-	-	-
Subphenotype of ARDS n (%) *								
Hypoinflammatory	1966 (74.1)	-	616 (72.4)	-	-	-	-	-
Hyperinflammatory	687 (25.9)	-	235 (27.6)	-	-	-	-	-
SOFA score day 1 Mean (SD)	9.39 (4.08)	-	9.55 (4.19)	8.69 (3.97)	9.2 (4.1)	-	8.69 (3.97)	-
Non respiratory SOFA score day 1 *	6.48 (3.96)	-	6.65 (4.06)	6.04 (3.87)	6.4 (4.0)	-	6.04 (3.87)	-
Ventilated on day 1 n (%)	2151 (81.1)	-	700 (82.3)	698 (82.0)	2849 (81.3)	-	698 (82.0)	-
Duration of invasive mechanical ventilation Mean (SD) *	12.0 (12.9)	-	12.2 (12.8)	10.6 (12.6)	11.7 (12.9)	-	10.6 (12.6)	-
ICU LOS Mean (SD)	14.2 (14.0)	6.2 (8.2)	12.7 (13.8)	6.2 (8.2)	13.8 (14.0)	6.2 (8.2)	12.7 (13.8)	6.2 (7.9)
ICU mortality n (%)	906 (34.2)	730 (13.8)	293 (34.4)	206 (24.2)	1112 (31.7)	1000 (14.3)	206 (24.2)	247 (14.5)
Hospital LOS Mean (SD) *	23.1 (20.8)	-	23.6 (20.7)	22.6 (20.7)	22.9 (20.8)	-	22.6 (20.7)	-
Hospital mortality n (%) *	1044 (39.4)	-	342 (40.2)	259 (30.4)	1303 (37.3)	-	259 (30.4)	-

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.

*Denotes variable with missing data. Further details of missing data are available in eTable-2a

Post matching standardised mean differences (SMDs) for the matching covariates in each model are shown in eTable-4 and were all < 0.05; empirical cumulative density function plots for matching covariates were also consistent with good balance (eFigure-2). Propensity score overlap following matching is shown for each model in eFigure-3.

ARDS: acute respiratory distress syndrome; AHRF: acute hypoxaemic respiratory failure; AHRF-UL: acute hypoxaemic respiratory failure with unilateral infiltrates only; Std Diff: standardised difference; SD: standard deviation; BMI: Body Mass Index; SOFA: sequential organ failure assessment; ICU: intensive care unit; LOS: length of stay; NMV: non-matched variable.

Table 2

Sensitivity analysis - Overall and subpopulation estimates of AF_{ARDS}, AF_{AHRF} and $AF_{AHRF-UL}$

	Model 1: AF_{ARDS} (non- AHRF controls)	**Model 2: AF_{ARDS} (AHRF-UL controls)**		**Model 3: AF_{AHRF} (non- AHRF controls)**	**Model 4: $AF_{AHRF-UL}$ (non-AHRF controls)**
Sensitivity analysis	***Unmatched analysis***	***Unmatched analysis***	***Matched analysis - hospital mortality as outcome***	***Unmatched analysis***	***Unmatched analysis***
Patients with ARDS/ AHRF	2653	2653	851	3504	851
Controls	8407	851	851	8407	8407
Overall AF	25.2% (22.7 – 27.6%)	22.3% (14.4 – 30.1%)	17.7% (7.7 – 27.6%)	26.5% (23.9 – 29.1%)	5.9% (4.1 – 7.7%)
PaO_2/FiO_2ratio (mmHg)					
>200	8.9% (4.5 – 13.4%)	10.7% (−1.6 – 23.0%)	25.8% (7.6 – 43.9%)	10.6% (6.3 – 15.0%)	2.5% (=2.5 – 7.5%)
100–200	17.2% (13.4 – 21.1%)	23.6% (13.2 – 34.0%)	3.1% (−13.7 – 19.9%)	18.9% (15.2 – 22.7%)	3.6% (1.3 – 8.5%)
<100	14.5% (10.7 – 18.5%)	33.9% (25.9 – 41.9%)	35.0% (18.9 – 51.2%)	15.6% (11.7 – 19.5%)	1.6% (−3.5% - 6.7%)
Maximum number of quadrants involved in first 48 hours					
One	-	-	-	3.9% (−1.0 – 8.8%)	3.9% (−1.0 – 8.8%)
Two	11.3% (7.0 – 15.6%)	9.7% (−2.9 – 22.4%)	12.0% (−5.3 – 29.4%)	12.8% (8.6 – 17.0%)	2.3% (−2.7 – 7.3%)
Three	10.8% (6.6 – 15.1%)	20.0% (9.7 – 30.2%)	18.3% (−1.8 – 38.5%)	10.9% (6.6% - 15.1%)	-
Four	18.8% (15.1 – 22.4%)	36.4% (28.2 – 44.6%)	22.3% (7.0 – 37.6%)	18.7% (15.1 – 22.4%)	-
Subphenotype					
Hypoinflammatory	18.3% (14.4 – 22.1%)	21.3% (10.2 – 32.4%)	14.1% (1.9 – 26.3%)	-	-
Hyperinflammatory	19.4% (15.9 – 23.0%)	31.9% (22.4 – 41.5%)	25.9% (7.4 – 44.4%)	-	-

Our primary analysis used matching without replacement with ICU mortality as the primary outcome measure. We repeated the analysis without matching in all four models to examine how matching – and therefore selection of controls, affected AF estimates. The matched analysis was also conducted using hospital mortality (instead of ICU mortality) as the outcome measure in Model-2.

AF: attributable fraction; CI; confidence interval; ARDS: acute respiratory distress syndrome; AHRF: acute hypoxaemic respiratory failure; AHRF-UL: acute hypoxaemic respiratory failure with unilateral infiltrates only