Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
CRITICAL CARE

Impact of differences in acute respiratory distress syndrome randomised controlled trial inclusion and exclusion criteria: systematic review and meta-analysis

Rohit Saha¹, Benjamin Assouline¹, Georgina Mason¹, Abdel Douiri²,³, Charlotte Summers⁴ and Manu Shankar-Hari⁵,⁶,*

¹Critical Care, King’s College Hospital NHS Foundation Trust, London, UK, ²School of Population Health & Environmental Sciences, King’s College London, London, UK, ³National Institute for Health Research Comprehensive Biomedical Research Centre, Guy’s and St Thomas’ NHS Foundation Trust, London, UK, ⁴Department of Medicine, University of Cambridge, Cambridge, UK, ⁵Critical Care, Guy’s and St Thomas’ NHS Foundation Trust, London, UK and ⁶School of Immunology & Microbial Sciences, King’s College London, London, UK

*Corresponding author. E-mail: manu.shankar-hari@kcl.ac.uk

Abstract

Background: Control-arm mortality varies between acute respiratory distress syndrome (ARDS) RCTs.

Methods: We systematically reviewed ARDS RCTs that commenced recruitment after publication of the American—European Consensus (AECC) definition (MEDLINE, Embase, and Cochrane central register of controlled trials; January 1994 to October 2020). We assessed concordance of RCT inclusion criteria to ARDS consensus definitions and whether exclusion criteria are strongly or poorly justified. We estimated the proportion of between-trial difference in control-arm 28-day mortality explained by the inclusion criteria and RCT design characteristics using meta-regression.

Results: A literature search identified 43 709 records. One hundred and fifty ARDS RCTs were included; 146/150 (97.3%) RCTs defined ARDS inclusion criteria using AECC/Berlin definitions. Deviations from consensus definitions, primarily aimed at improving ARDS diagnostic certainty, frequently related to duration of hypoxaemia (117/146; 80.1%). Exclusion criteria could be grouped by rationale for selection into strongly or poorly justified criteria. Common poorly justified exclusions included pregnancy related, age, and comorbidities (infectious/immunosuppression, hepatic, renal, and human immunodeficiency virus/acquired immunodeficiency syndrome). Control-arm 28-day mortality varied between ARDS RCTs (mean: 29.8% [95% confidence interval: 27.0–32.7%; I²=88.8%; τ²=0.02; P<0.01]), and differed significantly between RCTs with different PaO₂:FiO₂ ratio inclusion thresholds (26.6–39.9 kPa vs <26.6 kPa; P<0.01). In a meta-regression model, inclusion criteria and RCT design characteristics accounted for 30.6% of between-trial difference (P<0.01).

Conclusions: In most ARDS RCTs, consensus definitions are modified to use as inclusion criteria. Between-RCT mortality differences are mostly explained by the PaO₂:FiO₂ ratio threshold within the consensus definitions. An exclusion criteria framework can be applied when designing and reporting exclusion criteria in future ARDS RCTs.

Keywords: ARDS; exclusion; inclusion; mortality; randomised controlled trial

Received: 1 September 2020; Accepted: 21 February 2021

© 2021 British Journal of Anaesthesia. Published by Elsevier Ltd. All rights reserved.

For Permissions, please email: permissions@elsevier.com
Editor’s key points

- In this systematic review and meta-analysis, the authors identified modifications to acute respiratory distress syndrome definitions that are used to specify trial inclusion criteria.
- Variation in mortality between RCTs is accounted for by differences in selected PaO2:FiO2 ratio thresholds.
- Exclusion criteria between trials vary greatly, but can be adjudicated based on the rationale for selection.
- This framework can be used to select exclusion criteria in future RCTs and when deciding whether results from an RCT are useful in patients excluded from the RCT.

Inclusion criteria in acute respiratory distress syndrome (ARDS) RCTs are usually based either on the American–European Consensus Conference (AECC) definition 1 or the Berlin definition,2 which superseded the former. It is recognised that the difference in control-arm mortality between ARDS RCTs is related to the severity of hypoxaemia2 within the ARDS consensus definitions.1,2 However, there has been limited assessment of how components of the inclusion criteria that are not specified within the consensus definitions1,2 contribute towards the observed mortality differences between ARDS RCTs. These refinements of ARDS inclusion criteria are considered important for improving certainty of ARDS diagnosis. For example, the use of standardised ventilatory settings or confirmatory time periods before definitive diagnosis of ARDS has been proposed to select patients more likely to have ‘true’ ARDS.4,5

Furthermore, exclusion criteria vary between ARDS RCTs, excluded patients do not explain the difference in control-arm outcomes, and justification6 of exclusion criteria used in ARDS RCTs has not been assessed to date.

In this context, we tested the hypotheses that variations in inclusion criteria not specified within the ARDS consensus definitions could contribute to the differences in control-arm mortality in ARDS RCTs, and that developing an exclusion criteria justification framework for ARDS RCTs would inform design of future RCTs. Using a systematic review and meta-analysis of ARDS RCTs, we assessed the concordance of the inclusion criteria reported in RCTs with the ARDS consensus definitions,1,2 and estimated the proportion of between-trial variance in control-arm 28-day mortality explained by differences in the inclusion criteria and RCT characteristics. We then used the justification framework reported by Van Spall and colleagues6 to assess the exclusion criteria reported in ARDS RCTs.

Methods

Review protocol

This systematic review and meta-analysis was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019089703) and conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.7 The PRISMA checklist is available in the Supplementary data. We did not receive external funding.

Information sources

We searched MEDLINE, Embase, and the Cochrane central register of controlled trials from January 1, 1994 to October 31, 2020 with no language restrictions. We used subject headings and text-word terms to search for RCTs on ARDS and adults (Cochrane, McMaster, Robinson, and Dickersin clinical trial filters). The full MEDLINE electronic search strategy is presented in Supplementary Methods S1. We manually searched reference lists from published ARDS systematic reviews. Citations were saved in EndNote (Philadelphia, PA, USA) and duplicated records removed.

RCT selection

All citations were independently reviewed against our RCT selection criteria by at least two authors (RS, BA, and GM) using Rayyan QCRI.8 Potentially relevant full-text articles were reviewed and disagreements were resolved by consensus (RS, BA, and GM). We included RCTs in adult patients (>16 yr) with ARDS that commenced recruitment after publication of the AECC definition in March 1994. RCTs with a factorial design that were reported separately were considered as distinct RCTs. Crossover RCTs, where control-arm mortality could not be quantified, and articles published only in abstract form or foreign language were excluded. RCTs in patients with COVID-19 were also excluded. Further details of RCT selection criteria are available in Figure 1.

Data items

A preliminary data extraction form was piloted on 20 randomly selected RCTs by RS and BA. Based on feedback from this process, variables in the final data collection form were then amended for inter-observer reliability. Data were independently extracted by RS, BA, and GM from the following domains: RCT design, patient characteristics, inclusion criteria, exclusion criteria, intervention tested, and all reported mortality outcomes. RCT design characteristics included type of intervention, sponsorship and funding, number of participating centres, World Bank country income group (first author), year of publication, and number of patients in control group.

Inclusion criteria were defined as any variable used for the ARDS case definition by the RCT; these included consensus ARDS definition cited, radiographic criteria, assessment of cardiac involvement, PaO2:FiO2 (P:F) ratio threshold, PEEP threshold, and inclusion of invasively or noninvasively ventilated patients. All time criteria that specified inclusion into the RCT based on the duration of ARDS or ventilation were also extracted (time since intubation, time since onset of ARDS, time since symptom onset, and time since admission). In RCTs, where ARDS inclusion criteria were not explicitly listed, we assumed that criteria corresponded to the ARDS definition cited in the body of the text or references. Criteria limiting RCT eligibility of patients were treated as exclusion criteria and were extracted from the RCTs.

Risk of bias

RCTs were assessed for risk of bias for control-arm mortality outcomes using the Cochrane risk-of-bias tool.9 A funnel plot of standard error against control-arm mortality was used to assess for evidence of publication bias related to control-arm mortality (Supplementary Fig. S1). The analysis was not subsequently adjusted for bias.
Synthesis of results

We extracted 28-day control-arm mortality using GraphClick from uncensored cumulative mortality/survival curves, if not reported. In addition, 30-day mortality, reported in two RCTs, was combined with 28-day mortality for meta-analysis.

We assessed concordance of every element of the ARDS inclusion criteria reported to the corresponding consensus definitions cited by the authors. A summary of clinical criteria used to diagnose ARDS in consensus definitions is available in the Supplementary data. The \( P:F \) ratio thresholds reported in RCTs were regrouped into two categories: \( >26.6 \) to \( <39.9 \) and \( <26.6 \) kPa.1,2

To inform an exclusion criteria framework for future ARDS RCTs, all exclusion criteria were categorised, as described previously by Van Spall and colleagues.6 Additional categories were specified for acute illness severity, and barotrauma, and an exclusion criteria category based on lower age limit was removed (in keeping with our RCT selection criteria). The category ‘related to female gender’ was recoded to ‘pregnancy related’. They were then classified into ‘strongly justified’ and ‘poorly justified’ based upon the rationale for their selection, as described by Van Spall and colleagues.6 Further details of the classification scheme are available in Supplementary Tables S3 and S4.

Meta-analysis model

To study the variability in control-arm mortality between RCTs, we used a random-effects meta-analysis model with control-arm 28-day mortality as the dependent variable and a random intercept for each RCT. Distribution of control-arm mortality was assessed for normality using a quantile–quantile plot (Supplementary Fig. S3). As control-arm mortality was not normally distributed, proportions were transformed using the Freeman–Tukey double arc-sine method. Each RCT was weighted by the inverse of the sampling variance. A maximum likelihood estimator was used to estimate mean mortality (random-effects pooled estimate), between-trial standard deviation attributable to heterogeneity (\( \tau^2 \)), and the percentage of variance attributable to heterogeneity rather than chance (\( I^2 \)). Subgroup analyses were conducted for all ARDS RCT inclusion criteria (listed in Table 1) and specific RCT characteristics (year of publication, single vs multicentre, first author World Bank country income group, and sample size). To estimate the proportion of between-trial variance (\( R^2 \)) explained by ARDS inclusion criteria, they were all included as predictors in a meta-regression model. The RCT characteristics were treated as categorical predictors (as specified in Table 1) and were added to estimate additional impact.11 Variance inflation factors were calculated for all
Table 1 RCT design characteristics and specified inclusion criteria. ARDS, acute respiratory distress syndrome; CXR, chest radiograph; LA, left atrial; PAWP, pulmonary artery wedge pressure; P:F, PaO2:FiO2. *Inclusion criteria were not assessed individually for the four RCTs that used the composite Murray score to include patients.

A. RCT design characteristics Number (%) of RCTs, n = 150

| Type of intervention                                                                 | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| Mechanical ventilation strategies and respiratory care                              | 63 (42.0)  |
| Pharmacological RCTs                                                                | 80 (53.3)  |
| Fluid management strategies                                                         | 7 (4.7)    |

| Sponsorship and funding                                                             | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| Government or institutional funding                                                 | 80 (53.3)  |
| Partial/complete industry funding                                                   | 36 (24.0)  |
| Unknown                                                                              | 34 (22.7)  |

| Number of participating centres                                                     | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| Single                                                                               | 67 (44.7)  |
| Multiple                                                                            | 83 (55.3)  |
| National                                                                            | 31 (20.6)  |
| International                                                                       | 52 (34.7)  |

| World Bank country income group (first author)                                      | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| Middle                                                                              | 37 (24.7)  |
| High                                                                                | 113 (75.3) |

| Year of publication                                                                | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| 1996–2000                                                                           | 15 (10.0)  |
| 2001–2005                                                                           | 24 (16.0)  |
| 2006–2010                                                                           | 33 (22.0)  |
| 2011–2015                                                                           | 38 (25.3)  |
| 2016–2020                                                                           | 40 (26.7)  |

| Patients in control group                                                          | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| 0–25                                                                                | 61 (40.7)  |
| 26–50                                                                               | 33 (22.0)  |
| 51–100                                                                              | 16 (10.7)  |
| 101–200                                                                             | 20 (13.3)  |
| >200                                                                                | 20 (13.3)  |

| ARDS definition                                                                     | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| American-European Consensus Conference                                             | 118 (78.7) |
| Berlin                                                                              | 28 (18.7)  |
| Murray score                                                                        | 4 (2.6)    |

| Invasively ventilated patients only                                                 | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| Yes                                                                                 | 142 (94.7) |
| No                                                                                  | 6 (4.0)    |
| Unclear                                                                             | 2 (1.3)    |

B. Inclusion criteria

| P:F ratio (maximum threshold; kPa)                                                  | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| 26.6–39.9                                                                            | 64 (43.8)  |
| <39.9                                                                               | 4 (2.7)    |
| <250                                                                                | 1 (0.7)    |
| <22.5                                                                               | 63 (42.5)  |
| <26.6                                                                               | 1 (0.7)    |
| <26.6 or 39.9 depending on PEEP                                                    | 11 (8.2)   |
| <22.6                                                                               | 1 (0.7)    |
| <20.0                                                                               | 1 (0.7)    |
| <6.7 for >3 h or P:F <10.6 for >6 h <26.6 or 39.9 depending on PEEP                | 1 (0.7)    |

| Minimum P:F ratio threshold specified                                               | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| Minimum PEEP (cm H2O2) specified                                                   | 40 (24.7)  |
| 5                                                                                   | 10 (7.5)   |

| Description of radiographic findings                                               | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| Bilateral infiltrates on CXR                                                        | 112 (76.7) |
| In three or four quadrants                                                          | 6 (4.1)    |
| Bilateral infiltrates on CXR or CT                                                  | 27 (18.5)  |
| Non-aerated lung parenchyma on CT                                                   | 1 (0.7)    |

| Exclusion of cardiac involvement                                                   | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| No clinical evidence of LA                                                        | 121 (82.9) |
| Hypertension or PAWP <18 mm Hg                                                    | 25 (17.1)  |
| Not explained by cardiac failure or overload                                        | 156 (100)  |

| Illness duration before enrolment specified                                         | Number (%) |
|-------------------------------------------------------------------------------------|------------|
| Time since symptom onset                                                           | 34 (23.3)  |
| Time since ARDS onset                                                              | 66 (44.2)  |
| Time since intubation (maximum)                                                    | 29 (19.9)  |
| Time since intubation (minimum)                                                    | 7 (4.8)    |
| Time since admission                                                               | 3 (2.1)    |
| Confirmatory time period specified                                                  | 20 (13.7)  |
| FiO2 specified                                                                      | 12 (8.2)   |

No clinical evidence of LA 121 (82.9)
Hypertension or PAWP <18 mm Hg 25 (17.1)
Not explained by cardiac failure or overload 156 (100)

Illness duration before enrolment specified
- Time since symptom onset: 34 (23.3)
- Time since ARDS onset: 66 (44.2)
- Time since intubation (maximum): 29 (19.9)
- Time since intubation (minimum): 7 (4.8)
- Time since admission: 3 (2.1)
- Confirmatory time period specified: 20 (13.7)

FiO2 specified: 12 (8.2)

Sensitivity analysis

We report three sensitivity analyses. First, to assess whether lung-protective strategy was independently associated with mortality, we included this variable in our meta-regression model. As RCTs did not always explicitly state the use of a lung-protective strategy, we assumed that RCTs commencing recruitment after the publication of the ARDS Network lower vs. higher tidal volume study used a lung-protective strategy and vice versa. Second, we repeated the meta-regression with alternative mortality time points (i.e. ICU, hospital, and 60-day mortality) as an independent variable. Third, we excluded RCTs that did not specifically use a P:F ratio inclusion threshold of 26.6 or 39.9 kPa.

For all analyses, a P-value of <0.05 was considered significant. Analyses were performed in R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria) using the tidyr, dplyr, meta, and forestplot packages.

Results

RCT selection

The bibliographic database search identified 43 709 records, as of October 31, 2020. After excluding duplicates, amongst the 37 756 records screened, 304 records were eligible for full-text evaluation. After full-text evaluation, we excluded 157 records and included 147 RCTs from the database search and three further RCTs from hand searching published review articles, resulting in 150 unique ARDS RCTs published between 1994 and 2020 that met our selection criteria (Fig. 1). A summary of RCT characteristics is reported in Table 1.

Risk of bias within RCTs

One hundred and four (69.3%) of 150 RCTs, including all RCTs of mechanical ventilation and respiratory care, were at high risk of bias attributable to inadequate blinding of participants or personnel. Although we included only RCTs in our study, 58 (38.7%) of 150 RCTs either did not or inadequately described the methods for allocation concealment and random sequence generation. Risk of bias was unclear in these RCTs.

Lack of blinding of outcome assessors was not deemed to introduce bias, as mortality is an objective outcome. Twenty-one (14.0%) RCTs that did not report mortality outcomes were adjudicated to have a high risk of reporting bias, whereas predictors in the model to exclude multicollinearity. Model robustness was tested using a permutation test.
Fig 2. Risk of bias for mortality outcomes in ARDS RCTs. Domains were specified and adjudicated as per the Cochrane risk-of-bias tool. RCTs were divided by intervention type and ordered by year of publication. ARDS, acute respiratory distress syndrome.
Assessment of concordance of inclusion criteria to ARDS consensus definitions

The AECC definition was used in 117 of 150 (78.0%), 17–133 the Berlin definition in 29 of 150 (19.3%), 134–162 and the composite Murray score 162 in four RCTs 164–167 as ARDS inclusion criteria, resulting in 146 RCTs, where components of inclusion criteria were assessed further. Only three of 32 131–133 RCTs that commenced recruitment of patients after publication of the Berlin definition did not use it to specify RCT inclusion criteria. The most commonly reported P:F ratio inclusion thresholds, below which patients were included in the RCT, were <26.6 kPa (63/146; 43.2%) and <39.9 kPa (64/146; 43.8%) (Table 1). The P:F ratio maximum threshold was concordant with the Berlin definition in 26/29 (89.7%) RCTs 134–136,138–149,151,152,154–161 compared with 101/117 (86.3%) RCTs 139–34,36,38–44,46,50–74,76,78–85,88–109,111,112,114–130,133,137 that used the AECC definition. Bilateral chest infiltrates on the chest radiograph (CXR) were used in 118/146 (80.8%) RCTs. 17 Ten of 146 (6.8%) RCTs stipulated a confirmatory time period, between 30 min and 24 h, during which ARDS needed to persist for enrolment into the trial. Eight of these RCTs reported a confirmatory time period between 12 and 24 h. Although 94.7% (142/150) of RCTs were conducted in invasively ventilated patients, six (4.0%) included patients receiving noninvasive ventilation 137,138,139,151 and two (1.3%) did not clearly state how patients were being ventilated. 79,113

Assessment of deviation from ARDS consensus definitions

Deviations from the consensus criteria for P:F ratio were P:F <20.0 kPa (11/146; 7.5%), 35,37,45,47–49,77,78,113,153 P:F <33.3 kPa (4/146; 2.7%), 75,110,132,162 P:F <26.6 kPa with PEEP >5 cm H₂O or P:F <39.9 with PEEP >10 cm H₂O (1/146; 0.7%), 46 P:F <29.9 kPa (1/146; 0.7%). 18 P:F <22.6 kPa (1/146; 0.7%) 105 and P:F <6.7 kPa for >3 h or P:F <10.6 kPa for >6 h (1/146; 0.7%). 131

Ten of 146 (6.8%) RCTs specified an additional minimum P:F ratio threshold below which patients were excluded. 25,53,57,62,104,106,128,139,145,157 This minimum threshold varied from 8.0 to 26.6 kPa. Twelve (8.2%) RCTs specified standardised FiO₂ settings that ranged between 0.5 and 1.0. 56,62,42,47,48,55,61,62,120,123,139,158

Deviation from radiological criteria was noted in six (4.1%) RCTs 17,18,51,55,67,81 that stipulated the presence of infiltrates in more than three or four CXR quadrants, and one (0.7%) RCT 114 that used CT criteria only. Four (2.7%) RCTs 137–139,143 that used the Berlin definition instead used criteria from the AECC definition to exclude cardiac involvement. Amongst RCTs using the AECC definition, 22/117 (18.8%) 135–37,45–49,61,77,87,103,104,110,120,123,126,131 specified a minimum value for PEEP. In RCTs using the Berlin definition, 3/29 (10.3%) 147,150,158 specified PEEP >5 cm H₂O. One hundred and seventeen of 146 RCTs (80.1%) specified inclusion criteria related to illness duration before enrolment. Time since ARDS onset was specified in 66/146 (45.2%; median: 2 days; range: 1–7) RCTs 17–21,28–34,36,42–45,48,49,52,53,61,64,66–71,78–81,84,85,87,89,97,99,102–104,106,107,110,112,118,123,125,130–135,138,141,142,147,148,150,153,161 Maximum time since intubation was specified in 29/146 (19.9%; median: 3 days; range: 1–10) RCTs. 75,69,70,91,105,113,140 Time since admission was specified in three (2.1%; median: 2 days; range: 2–2) RCTs. 71,56,59

Twenty (13.7%) RCTs 54,55,31,37,42,45,49,90,94,96,105,114–117,120,131,132,135,158 stipulated a confirmatory time period, between 30 min and 24 h, during which ARDS needed to persist for enrolment into the trial. Eight of these RCTs reported a confirmatory time period between 12 and 24 h. Although 94.7% (142/150) of RCTs were conducted in invasively ventilated patients, six (4.0%) included patients receiving noninvasive ventilation 137,138,139,151 and two (1.3%) did not clearly state how patients were being ventilated. 79,113

Assessment of between-trial variance (I²) in control-arm 28-day mortality and impact of differences in inclusion criteria

Mortality outcomes were reported in 125 of 146 (85.6%) RCTs (Supplementary Fig. S2). The 28-day mortality was reported in 73 (50.0%) RCTs, 30-day mortality in two, and extrapolated from a further nine RCTs using GraphClick, resulting in 84 RCTs with primary outcome for meta-analysis. There was significant variance in control-arm mortality at 28 days between RCTs, with a random effects estimated mean mortality of 29.8% (95% confidence interval [CI]: 27.0–32.7%); range: 3.6–69.7%; I² = 88.8% (84.4–92.3%); τ² = 0.015 (0.011–0.023; P < 0.01) (Fig. 3a; Supplementary Figure S4).

The 28-day mortality in RCTs that used a P:F ratio inclusion threshold of <26.6 kPa (35.1%; 95% CI: 31.8–38.4%) was higher compared with RCTs using a P:F ratio inclusion threshold between 26.6 and 39.9 kPa (25.7%; 95% CI: 21.9–29.7%). Mean mortality did not significantly differ between RCTs with other additional inclusion criteria differences: specification of minimum P:F ratio threshold below which patients were excluded, definition of imaging findings, definition for exclusion of cardiac involvement, time windows for inclusion (symptom onset, ARDS onset, intubation, admission, and confirmatory time period), and specification of PEEP >5 cm H₂O or FiO₂ (Fig. 3a).

Within-trial variance that cannot be explained by study-level variables accounted for 11.4% (95% CI: 7.7–16.0%) of total variance. Therefore, 88.6% (95% CI: 84.0–92.3%) of total variance was a result of between-trial variance (I²). A meta-regression model, including all inclusion criteria variables and RCT design characteristics, accounted for a total of 30.6% (95% CI: 17.7–43.5%) of the between-trrial variance (R²).

The P:F ratio inclusion threshold was the only variable in the model significantly associated with control-arm 28-day mortality (P < 0.01). Therefore, 69.4% (95% CI: 56.5–82.3%) of the between-trial variance remained unexplained by inclusion criteria differences (Fig. 3b; Supplementary Tables S5 and S6).

13 (8.7%) RCTs that did not specify the mortality time point were felt to be at unclear risk (Fig. 2).
| Inclusion criteria                                                                 | Trials | Patients | 28-day control arm mortality (%) | 95% CI | Interaction P-value |
|-----------------------------------------------------------------------------------|--------|----------|----------------------------------|--------|---------------------|
| **Overall**                                                                        | 84     | 10952    | 29.8                             |        |                     |
| **Consensus definition**                                                           |        |          |                                  |        |                     |
| Maximum $P:F$ ratio threshold (kPa)                                                |        |          |                                  |        |                     |
| 26.6–39.9                                                                         | 40     | 6105     | 25.7                             |        | 21.9–29.7 <0.01     |
| <26.6                                                                             | 44     | 4847     | 35.1                             |        | 31.8–38.4           |
| Minimum $P:F$ ratio threshold specified                                           |        |          |                                  |        |                     |
| No                                                                                 | 79     | 10767    | 30.6                             |        | 27.9–33.5 0.41     |
| Yes                                                                                | 5      | 185      | 24.5                             |        | 12.3–39.3           |
| **Description of radiographic findings**                                           |        |          |                                  |        |                     |
| Bilateral infiltrates on CXR                                                       | 63     | 8925     | 31.5                             |        | 28.5–34.6 0.33     |
| Bilateral infiltrates on three or four quadrants on CXR                           | 4      | 317      | 25.7                             |        | 16.3–36.4           |
| Bilateral infiltrates on CXR or CT                                                 | 17     | 1710     | 26.9                             |        | 20.0–34.3           |
| Exclusion of cardiac involvement                                                   |        |          |                                  |        |                     |
| No clinical evidence of LA hypertension/PAWP <18 mm Hg                            | 69     | 9373     | 31.3                             |        | 28.2–34.5 0.13     |
| Not explained by cardiac failure or overload                                      | 15     | 1579     | 26.1                             |        | 20.5–32.1           |
| PEEP >5 cm H$_2$O                                                                  |        |          |                                  |        |                     |
| No                                                                                 | 75     | 9725     | 29.7                             |        | 26.8–32.7 0.17     |
| Yes                                                                                | 9      | 1227     | 35.4                             |        | 27.9–43.3           |
| **Time since symptom onset**                                                       |        |          |                                  |        |                     |
| No                                                                                 | 63     | 8354     | 31.0                             |        | 27.9–34.1 0.46     |
| Yes                                                                                | 21     | 2598     | 28.4                             |        | 22.5–34.7           |
| **Additional criteria**                                                            |        |          |                                  |        |                     |
| Time since ARDS onset                                                              |        |          |                                  |        |                     |
| No                                                                                 | 40     | 3336     | 31.7                             |        | 27.1–36.6 0.36     |
| Yes                                                                                | 44     | 7616     | 29.1                             |        | 26.0–32.3           |
| **Time since intubation (maximum)**                                               |        |          |                                  |        |                     |
| No                                                                                 | 56     | 7795     | 31.3                             |        | 27.8–34.9 0.16     |
| Yes                                                                                | 20     | 3157     | 27.7                             |        | 24.1–31.4           |
| Time since intubation (minimum)                                                    |        |          |                                  |        |                     |
| No                                                                                 | 80     | 10651    | 30.1                             |        | 27.3–33.0 0.51     |
| Yes                                                                                | 4      | 301      | 35.7                             |        | 20.2–53.0           |
| **Time since admission**                                                           |        |          |                                  |        |                     |
| No                                                                                 | 82     | 10906    | 30.0                             |        | 27.2–32.9 0.03     |
| Yes                                                                                | 2      | 46       | 45.8                             |        | 31.9–60.0           |
| **Confirmatory time period**                                                       |        |          |                                  |        |                     |
| No                                                                                 | 73     | 9110     | 29.7                             |        | 26.7–32.7 0.25     |
| Yes                                                                                | 11     | 1842     | 34.2                             |        | 27.2–41.6           |
| **FiO2**                                                                           |        |          |                                  |        |                     |
| No                                                                                 | 73     | 9643     | 30.9                             |        | 27.9–34.0 0.32     |
| Yes                                                                                | 11     | 1309     | 27.0                             |        | 20.4–34.1           |
| **RCT characteristics**                                                            |        |          |                                  |        |                     |
| Year of publication                                                                |        |          |                                  |        |                     |
| 1996–2000                                                                         | 8      | 824      | 33.1                             |        | 29.9–36.3 0.51     |
| 2001–2005                                                                         | 16     | 1503     | 31.8                             |        | 24.9–39.2           |
| 2006–2010                                                                         | 15     | 2953     | 30.7                             |        | 24.7–37.0           |
| 2011–2015                                                                         | 19     | 2906     | 28.4                             |        | 23.6–33.4           |
| 2016–2020                                                                         | 26     | 2766     | 28.8                             |        | 23.4–34.6           |
| World bank country income group (first author)                                     |        |          |                                  |        |                     |
| Middle                                                                             | 17     | 1250     | 31.3                             |        | 23.5–40.9 0.68     |
| High                                                                              | 67     | 9702     | 29.9                             |        | 27.3–32.7           |
| Multicentre trial                                                                  |        |          |                                  |        |                     |
| Yes                                                                                | 59     | 10129    | 29.6                             |        | 26.8–32.5 0.43     |
| No                                                                                 | 25     | 823      | 32.6                             |        | 25.8–39.9           |
| **Patients in control group**                                                      |        |          |                                  |        |                     |
| 0–25                                                                               | 19     | 320      | 33.1                             |        | 26.1–40.5 0.17     |
| 26–50                                                                              | 17     | 540      | 36.1                             |        | 28.7–43.7           |
| 51–100                                                                             | 12     | 876      | 32.1                             |        | 24.3–40.4           |
| 101–200                                                                            | 16     | 2205     | 24.6                             |        | 18.6–31.2           |
| >200                                                                               | 20     | 7011     | 29.1                             |        | 25.9–32.5           |
Assessment of exclusion criteria and justification framework

Of 150 RCTs, 141 (94.0%) reported exclusion criteria. Of the nine RCTs that did not report exclusion criteria, five were published after the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines. Definitions of exclusion criteria varied greatly between RCTs (Supplementary Table S4). For example, hepatic disease was variably defined within RCTs based on specific factors, including bilirubin level, transaminase concentration, Child-Pugh grade, and evidence of cirrhosis, or non-specifically as chronic liver disease or acute liver failure (Supplementary Table S4).

The exclusion criteria in ARDS RCTs were then categorised based on the justification framework proposed by Van Spall and colleagues (Fig. 4). To do this evaluation, we had to modify this framework in four ways: (i) by including two additional but important ARDS specific categories: acute illness severity and barotrauma; (ii) changing the domain ‘related to female gender’ to ‘pregnancy related’ to avoid conflating the two issues; (iii) by not including a lower age limit category, as we were assessing adult ARDS RCTs; and (iv) by not including the ‘potentially justified’ category. As defined by Van Spall and colleagues, potentially justified criteria relate to potential patient non-adherence to intervention or follow-up that cannot be classified as poorly/strongly justified. We did not identify any potentially justified criteria in ARDS RCTs, and therefore opted to simplify the justification framework.

The exclusion criteria in RCTs with strong justification were comorbidities neurological (73/78; 93.6%), respiratory (70/70; 100%), cardiac (55/55; 100%), life expectancy (long-term prognosis [33/33; 100%]; short-term prognosis [41/41; 100%]), acute illness related (acute illness severity [58/58; 100.0%]; barotrauma [34/34; 100%]), participation in another trial (55/55; 100%), inability to obtain consent (46/46; 100%), and medication related (45/45; 100%) (Fig. 4; Supplementary Table S3). The exclusion criteria in RCTs with poor justification were pregnancy related (76/83 [80.5%]; upper age limit [17/17; 100%]) and the following comorbidities: infectious/immunosuppression (50/50; 100%), hepatic (49/61; 80.3%), renal (27/34; 79.4%), and human immunodeficiency virus/acquired immunodeficiency syndrome (15/16; 93.8%) (Fig. 4; Supplementary Table S4).

Sensitivity analysis

Between-trial and overall relationships between inclusion criteria and mortality remained consistent and unchanged after the inclusion of lung-protective strategy as a variable in the meta-regression model. Similarly, meta-regression with mortality time points (28-day/60-day/ICU/hospital mortality) as an independent categorical variable, or exclusion of RCTs...
Fig 4. Categories of exclusion criteria reported in ARDS RCTs. ARDS, acute respiratory distress syndrome; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome.
that used a P:F ratio inclusion threshold other than 26.6 or 39.9 did not alter findings. Univariate and multivariate models for these analyses are reported in Supplementary Figures S5–S7.

Discussion

Although 97% of ARDS RCTs use consensus definitions for inclusion criteria, we observed deviations from the consensus definitions that were primarily aimed to increase the certainty of ARDS diagnosis, such as duration of hypoxaemia after ventilation, in more than 80% of ARDS RCTs. Importantly, the transition from the AECC definition to the Berlin definition has improved overall concordance between individual elements of the RCT inclusion criteria and the consensus definition. As predicted, there was significant variance in control-arm mortality. However, these additional refinements of ARDS inclusion criteria did not explain the observed variance, over and above the effect of severity of hypoxaemia on control-arm mortality. We illustrate that the justification framework reported by Van Spall and colleagues is a feasible tool to assess the exclusion criteria reported in ARDS RCTs, the tool requires modification, and that many exclusion criteria in ARDS RCTs were poorly justified. We provide a novel assessment of the concordance of inclusion criteria in ARDS RCTs to the ARDS consensus definitions and its impact on control-arm mortality.

For assessing the impact of inclusion criteria differences, we explored how consensus definitions were modified as ARDS RCT inclusion criteria and assessed individual contributions to outcome. Our finding that there is significant heterogeneity in control-arm mortality is consistent with a previous meta-analysis that included RCTs between 1984 and 2006. Importantly, deviations from the consensus criteria, such as use of standardised ventilator settings for PEEP and FiO2 when defining ARDS, delayed reassessment of patients to confirm ARDS diagnosis (confirmatory period), and classification based on time of onset into early or late ARDS was thought to improve ARDS diagnosis or enrich for adverse outcome. These had negligible impact on 28-day mortality over and above the P:F ratio strata. Our analyses highlight that severity of hypoxaemia is the only inclusion criterion that reliably stratifies ARDS patients by risk of death, which is consistent with the predictive validity analyses reported in the Berlin ARDS definition.

We also highlight that the justification framework proposed by Van Spall and colleagues requires modification for use in ARDS RCTs. Based on our analysis, we propose two classes of exclusion criteria, namely, strongly justified and poorly justified, and that exclusion criteria could be linked to the intervention tested. This proposal has validity, as exclusion criteria that we categorised as poorly justified in ARDS RCTs have also been highlighted in non-critical care RCTs. For example, instead of blanket exclusion of women of reproductive age attributable to pregnancy-related risk, the framework we propose would consider whether excluding pregnant patients was strongly or poorly justified for the specific intervention that is being trialled. If the intervention does not have teratogenic properties (e.g. mechanical ventilation), then pregnancy need not be an exclusion. Extending this argument, we could also consider whether results from a trial are useful when managing patients with an exclusion criterion in that trial. This issue is seldom considered during clinical practice.

Aside from eligibility criteria, heterogeneity in mortality outcomes between RCTs can be attributed to setting and design characteristics, such as geographic and socio-economic population differences, unreported exclusion of patients, and differences in post-randomisation care between RCTs.

Strengths and limitations

We report the first assessment of ARDS RCT eligibility criteria as a reason for between-trial differences in control-arm mortality. We pre-registered with PROSPERO and reported in accordance with PRISMA recommendations. Our exclusion criteria framework could be used for RCT design and prospective reporting. This would inform whether the results of a specific ARDS RCT would apply to patients with one or more of the RCT exclusion criteria, but without a known risk of harm from the intervention.

We applied the Cochrane risk-of-bias tool to explore bias between RCTs, but did not alter our analysis to account for this. This was because the primary outcome, control-arm mortality, is unlikely to be influenced by risk of bias. As we do not know which exclusion criteria were specifically met by patients excluded from RCTs, we were unable to assess their impact on mortality. We used year of publication rather than year of enrolment as the time variable in our analysis because the latter was not always reported. In a proportion of RCTs, where individual components of the inclusion criteria were not specified, inclusion criteria were assumed to correspond to the stated definition. We specifically focused on 28-day mortality, which was not available in 66 RCTs, and grouped RCTs by P:F ratio inclusion threshold (26.6–39.9 and <26.6) to assess concordance with consensus definitions. Both issues are addressed within our sensitivity analyses, which were consistent with our main analysis.

We need to ascertain whether our modified exclusion criteria framework is implementable in future ARDS RCTs. Furthermore, it will be important to consider how to record multiple exclusion criteria in a single patient, within the CONSORT framework, which can be explored using a clinical database. Various definitions of exclusion criteria can be simulated to examine their impact upon an RCT population.

Conclusion

In most ARDS RCTs, the consensus definitions are modified to use as inclusion criteria. Most of the between-RCT differences in mortality are accounted for by the P:F ratio threshold within the consensus definitions. Exclusion criteria definitions were different between RCTs. We provide a simplified exclusion criteria framework to be applied when designing and reporting exclusion criteria in future ARDS RCTs.

Authors’ contributions

Study conception/design: RS, MS-H
Development of search strategy: RS, MS-H
Literature review: RS, BA, GM
Data extraction: RS, BA, GM
Data analysis: RS
Data interpretation: all authors
Drafting of paper: RS, MS-H
Critical revision and approval of paper: all authors
All authors confirm the accuracy and integrity of the work. RS takes responsibility for the integrity of the work as a whole, from inception to published paper.

Acknowledgements
The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health and Social Care.

Declarations of interest
The authors declare that they have no conflicts of interest.

Funding
Wellcome Trust to CS; Medical Research Council to CS; National Institute of Health Research Cambridge Biomedical Research Centre to CS; National Institutes of Health to CS; British Heart Foundation to CS; GlaxoSmithKline to CS; AstraZeneca to CS; Bristol Myers Squibb to CS; National Institute of Health Research Clinician Scientist Award (NIHR-CS-2016-16-011) to MS-H.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.02.027.

References
1. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149: 818–24
2. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012; 307: 2526–33
3. Phua J, Badia JR, Adhikari NKJ, et al. Has mortality from acute respiratory distress syndrome decreased over time? Am J Respir Crit Care Med 2009; 179: 220–7
4. Villar J, Perez-Mendez L, Belda J, et al. An early PEEP/FIO₂ trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2007; 176: 795–804
5. Villar J, Perez-Mendez L, Blanco J, et al. A universal definition of ARDS: the PaO₂/FIO₂ ratio under a standard ventilatory setting—a prospective, multicenter validation study. Intensive Care Med 2013; 39: 583–92
6. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA 2007; 297: 1233–40
7. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the FRISMA statement. PLoS Med 2009; 6, e1000097
8. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev 2016; 5: 210
9. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928
10. Flower A, McKenna JW, Upreti G. Validity and reliability of GraphClick and DataThief III for data extraction. Behav Modif 2016; 40: 396–413
11. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to meta-analysis. Chichester: Wiley; 2009
12. R Foundation for Statistical Computing. R Development Core Team. R: a language and environment for statistical computing 2019. http://www.R-project.org/. [Accessed 23 December 2020]
13. Wickham H, Henry L. tidy: tidy messy data. R package version 100. https://github.com/tidyverse/tidy. Last accessed: 23 Dec 2020.
14. Wickham H, François R, Henry L, Müller K. dplyr: a grammar of data manipulation. R package version 083 2019. https://github.com/tidyverse/dplyr. [Accessed 23 December 2020]
15. Schwarzer G. meta: an R package for meta-analysis. R Neu 2007; 7: 40–5. https://github.com/guido-s/meta/. [Accessed 23 December 2020]
16. Gordon M, Lumley T. forestplot: advanced forest plot using ‘grid’ graphics. R package version 1.9 2019. https://github.se/packages/. [Accessed 23 December 2020]
17. Abraham E, Baughman R, Fletcher E, et al. Liposomal prostaglandin E1 (TLC C-53) in acute respiratory distress syndrome: a controlled, randomized, double-blind, multicenter clinical trial. Crit Care Med 1999; 27: 1478–85
18. Abraham E, Park YC, Covington P, Conrad SA, Schwartz M. Liposomal prostaglandin E1 in acute respiratory distress syndrome: a placebo-controlled, randomized, double-blind, multicenter clinical trial. Crit Care Med 1996; 24: 10–5
19. The ARDS Network Authors for the ARDS Network. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome. JAMA 2000; 283: 1995–2002
20. The ARDS Clinical Trials Network. National Heart, Lung, and Blood Institute, National Institutes of Health. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. Crit Care Med 2002; 30: 1–6
21. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342: 1301–8
22. Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Adaptive support ventilation for complete ventilatory support in acute respiratory distress syndrome: a pilot, randomized controlled trial. Respir Med 2013; 18: 1108–15
23. Al Masry A, Boules M, Boules N, Eibed R. Optimal method for selecting PEEP level in ALI/ARDS patients under mechanical ventilation. J Egypt Soc Parasitol 2012; 42: 359–72
24. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO₂ removal versus ‘conventional’ protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med 2013; 39: 847–56
25. Bein T, Zimmermann M, Schiewe-Langgartner F, et al. Continuous lateral rotational therapy and systemic inflammatory response in posttraumatic acute lung injury: results from a prospective randomised study. Injury 2012; 43: 1892–7
26. Bein TH, Reber A, Ploner F, Taeger K, Jauch KW. Continuous axial rotation and pulmonary fluid balance in acute lung injury. Clin Intensive Care 2000; 11: 307–10

27. Bollen CW, van Well GT, Sherry T, et al. High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]. Crit Care 2005; 9: R430–9

28. Braunschweig CA, Sheean PM, Peterson SJ, et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT). JPN J Parenteral Enteral Nutr 2015; 39: 13–20

29. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004; 351: 327–36

30. Brower RG, Shanholz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med 1999; 27: 1492–8

31. Cavalcanti AB, Suzumura EA, Laranjeira LN, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017; 318: 1335–45

32. Chung FT, Lee CS, Lin SM, et al. Alveolar recruitment maneuver attenuates extravascular lung water in acute respiratory distress syndrome. Medicine (Baltimore) 2017; 96, e7627

33. Cornet AD, Groeneveld AB, Hofstra JJ, et al. Recombinant human activated protein C in the treatment of acute respiratory distress syndrome: a randomized clinical trial. PLoS One 2014; 9, e90983

34. Craig TR, Duffy MJ, Shyamsundar M, et al. A randomized clinical trial of hydroxyethylmethylacrylate-coenzyme a reductase inhibition for acute lung injury (the HARP study). Am J Respir Crit Care Med 2011; 183: 620–6

35. Cuthbertson BH, Galley HF, Webster NR. Effect of inhaled nitric oxide on key mediators of the inflammatory response in patients with acute lung injury. Crit Care Med 2000; 28: 1736–41

36. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998; 26: 15–23

37. Demory D, Michelet P, Arnal JM, et al. High-frequency oscillatory ventilation following prone positioning prevents a further impairment in oxygenation. Crit Care Med 2007; 35: 106–11

38. Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 2002; 166: 801–8

39. Domenighetti G, Suter PM, Schaller M-D, Ritz R, Perret C. Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. J Crit Care 1997; 12: 177–82

40. Elamin EM, Miller AC, Ziad S. Immune enteral nutrition can improve outcomes in medical-surgical patients with ARDS: a prospective randomized controlled trial. J Nutr Disord Ther 2012; 2: 109

41. Esteban A, Alia I, Gordo F, et al. Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. Chest 2000; 117: 1690–6

42. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013; 368: 795–805

43. Fernandez R, Trenchs X, Klamburg J, et al. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. Intensive Care Med 2008; 34: 1487–91

44. Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006; 34: 2749–57

45. Gaimnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 2004; 32: 113–9

46. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001; 345: 568–73

47. Gerlach H, Keh D, Semmerow A, et al. Dose–response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. Am J Respir Crit Care Med 2003; 167: 1008–15

48. Guerin C, Reynier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013; 368: 2159–68

49. Guervilly C, Forel JM, Hraietch S, Roch A, Talmon D, Papazian L. Effect of high-frequency oscillatory ventilation on esophageal and transpulmonary pressures in moderate-to-severe acute respiratory distress syndrome. Ann Intensive Care 2016; 6: 84

50. Guoshou Z, Chengye Z, Zhihui L, Jinlong L. Effects of high dose of anisodamine on the respiratory function of patients with traumatic acute lung injury. Cell Biochem Biophys 2013; 66: 365–9

51. Gupta A, Govil D, Bhatnagar S, et al. Efficacy and safety of parenteral omega 3 fatty acids in ventilated patients with acute lung injury. Indian J Crit Care Med 2011; 15: 108–13

52. Heard SO, Longtine K, Toth I, Puyana JC, Potenza B, Smyrnios N. The influence of liposome-encapsulated prostaglandin E1 on hydrogen peroxide concentrations in the exhaled breath of patients with the acute respiratory distress syndrome. Anesth Analg 1999; 89: 353–7

53. Hirschl RB, Croce M, Gore D, et al. Prospective, randomized, controlled pilot study of partial liquid ventilation in adult acute respiratory distress syndrome. Am J Respir Crit Care Med 2002; 165: 781–7

54. Hodgson CL, Tuxen DV, Davies AR, et al. A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. Crit Care 2011; 15: R133

55. Hu W, Lin CW, Liu BW, Hu WH, Zhu Y. Extravascular lung water and pulmonary arterial wedge pressure for fluid management in patients with acute respiratory distress syndrome. Multidiscip Respir Med 2014; 9: 3

56. Hua F, Wang X, Zhu L. Terlipressin decreases vascular endothelial growth factor expression and improves
oxygenation in patients with acute respiratory distress syndrome and shock. J Emerg Med 2013; 44: 434–9

57. Huang SR, Ma AY, Liu Y, Qu Y. Effects of inflammatory factors including plasma tumor necrosis factor-alpha in the clinical treatment of acute respiratory distress syndrome. Oncol Lett 2017; 13: 5016–20

58. Huh JW, Jung H, Choi HS, Hong SB, Lim CM, Koh Y. Efficacy of positive end-expiratory pressure titration after the alveolar recruitment manoeuvre in patients with acute respiratory distress syndrome. Crit Care 2009; 13: R22

59. Iannuzzi M, De Sio A, De Robertis E, Piazza O, Servillo G, Huh JW, Jung H, Choi HS, Hong SB, Lim CM, Koh Y. Efficacy of positive end-expiratory pressure titration after the alveolar recruitment manoeuvre in patients with acute respiratory distress syndrome. Crit Care 2009; 13: R22

60. Kacmarek RM, Villar J, Sulemanji D, et al. Open lung approach for the acute respiratory distress syndrome. Crit Care Med 2016; 44: 32–42

61. Kacmarek RM, Wiedemann HP, Lavin PT, Wedel MK, Tutuncu AS, Slutsky AS. Partial liquid ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2006; 173: 882–9

62. Kadot Y, Hinohara H, Kunimoto F, et al. Pilot study of ONO-5046 in patients with acute respiratory distress syndrome. Anesth Analg 2004; 99: 872–7

63. Kesecioglu J, Beale R, Stewart TE, et al. Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2009; 180: 989–94

64. Khan A, Benthin C, Zeno B, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 2017; 21: 234

65. Krenn K, Lucas R, Croize A, et al. Inhaled AP301 for treatment of pulmonary edema in mechanically ventilated patients with acute respiratory distress syndrome: a phase IIa randomized placebo-controlled trial. Crit Care 2017; 21: 194

66. Liu KD, Levitt J, Zhuo H, et al. Randomized clinical trial of activated protein C for the treatment of acute lung injury. Am J Respir Crit Care Med 2008; 178: 618–23

67. Mancebo J, Fernández R, Blanch L, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med 2006; 173: 1233–9

68. Mao Z, Wang H. Effects of Xuanbai Chengqi decoction on lung compliance for patients with exogenous pulmonary acute respiratory distress syndrome. Drug Des Devel Ther 2016; 10: 793–8

69. Martin GS, Mangialardi RJ, Wheeler AP, Dupont WD, Morris JA, Bernard GR. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. Crit Care Med 2002; 30: 2175–82

70. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 2005; 33: 1681–7

71. Mascians J, Iglesias R, Bermejo B, Picó M, Rodríguez-Roisin R, Planas M. Gas exchange and pulmonary haemodynamic responses to fat emulsions in acute respiratory distress syndrome. Intensive Care Med 1998; 24: 918–23

72. Matthay MA, Brower RG, Carson S, et al. Randomized, placebo-controlled clinical trial of an aerosolized β2-agonist for treatment of acute lung injury. Am J Respir Crit Care Med 2011; 184: 561–8

73. McAuley DF, Laffey JG, O’Kane CM, et al. Simvastatin in the acute respiratory distress syndrome. N Engl J Med 2014; 371: 1695–703

74. McAuley DF, Cross LM, Hamid U, et al. Keratinocyte growth factor for the treatment of the acute respiratory distress syndrome (KARE): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Respir Med 2017; 5: 484–91

75. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299: 637–45

76. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007; 131: 954–63

77. Mentzelopoulos SD, Malachias S, Zintzaras E, et al. Intermittent recruitment with high-frequency oscillation/tracheal gas insufflation in acute respiratory distress syndrome. Eur Respir J 2012; 39: 635–47

78. Mercat A, Richard JC, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299: 646–55

79. Mojtahedzadeh M, Vazin A, Najafi A, Khalilzadeh A, Abdollahi M. The effect of furosemide infusion on serum epidermal growth factor concentration after acute lung injury. J Infus Nurs 2005; 28: 188–93

80. Morelli A, Teboul J-L, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med 2006; 34: 2287–93

81. Morris PE, Papadakos P, Russell JA, et al. A double-blind placebo-controlled study to evaluate the safety and efficacy of L-2-oxothiazolidine-4-carboxylic acid in the treatment of patients with acute respiratory distress syndrome. Crit Care Med 2008; 36: 782–8

82. Najafi A, Mojtahedzadeh M, Mahmoodpoor A, et al. Effect of N-acetylcysteine on microalbuminuria in patients with acute respiratory distress syndrome. Arch Med Sci 2009; 5: 408–14

83. Nemer SN, Caldeira RJ, Azeredo LM, et al. Alveolar recruitment maneuver in patients with subarachnoid hemorrhage and acute respiratory distress syndrome: a comparison of 2 approaches. J Crit Care 2011; 26: 22–7

84. Oczenski W, Hormann C, Keller C, et al. Recruitment maneuvers after a positive end-expiratory pressure trial do not induce sustained effects in early adult respiratory distress syndrome. Anesthesiology 2004; 101: 620–5

85. Ortolani O, Conti A, Gaudio A, Masi M, Novelli G. Protective effects of N-acetylcysteine and rutin on the lipid peroxidation of the lung epithelium during the adult respiratory distress syndrome. Shock 2000; 13: 14–8

86. Paine 3rd R, Standiford TJ, Dechert RE, et al. A randomized trial of recombinant human granulocyte-macrophage colony stimulating factor for patients with acute lung injury. Crit Care Med 2012; 40: 90–7

87. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363: 1107–16
88. Parish M, Valiyi F, Hamishehkar H, et al. The effect of omega-3 fatty acids on ARDS: a randomized double-blind study. *Adv Pharm Bull* 2014; 4: 555–61
89. Perkins GD, Gates S, Park D, et al. The beta agonist lung injury trial prevention. A randomized controlled trial. *Am J Respir Crit Care Med* 2014; 189: 674–83
90. Pintado MC, de Pablo R, Trascasa M, et al. Individualized PEEP setting in subjects with ARDS: a randomized controlled pilot study. *Respir Care* 2013; 58: 1416–23
91. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999; 282: 54–61
92. Rice TW, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011; 306: 1574–81
93. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012; 307: 795–803
94. Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2003; 290: 2713–20
95. Ryugo M, Sawa Y, Takano H, et al. Effect of a polymorphonuclear elastase inhibitor (sivelestat sodium) on acute lung injury after cardiopulmonary bypass: findings of a double-blind randomized study. *Surg Today* 2006; 36: 321–6
96. Sabater, Masclans J, Sacanell J, Chacon P, Sabin P, Planas M. Effects on hemodynamics and gas exchange of omega-3 fatty acid-enriched lipid emulsion in acute respiratory distress syndrome (ARDS): a prospective, randomized, double-blind, parallel group study. *Lipids Health Dis* 2008; 7: 39
97. Soltan-Sharif MS, Mojtabazadeh M, Najafi A, et al. Improvement by N-acetylcysteine of acute respiratory distress syndrome through increasing intracellular glutathione, and extracellular thiols molecules and antioxidant power: evidence for underlying toxicological mechanisms. *Hum Exp Toxicol* 2007; 26: 697–703
98. Sharaf M, El-Hantery M, Noaman M, Abel-Salam Y. Biphasic intermittent positive airway pressure ventilation versus conventional ventilation in acute respiratory distress syndrome and acute lung injury. *Trends Med Res* 2012; 7: 43–52
99. Shariatpanahi ZV, Taleban FA, Mokhtari M, Shahbazi S. Ginger extract reduces delayed gastric emptying and nosocomial pneumonia in adult respiratory distress syndrome patients hospitalized in an intensive care unit. *J Crit Care* 2010; 25: 647–50
100. Shirai K, Yoshida S, Matsumaru N, Toyota I, Ogura S. Effect of enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with sepsis-induced acute respiratory distress syndrome. *J Intensive Care* 2015; 3: 24
101. Singer P, Theilla M, Fisher H, Gibstein L, Grozovsky E, Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Crit Care Med* 2006; 34: 1033–8
102. Smirkin AA, Gaidukov KM, Bjertnaes LJ, Kirov MY. Recruitment test and surfactant therapy in patients with acute lung injury. *Crit Care Res Pract* 2012; 2012: 428798
103. Spragg RG, Lewis JF, Walmsrath HD, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2003; 167: 1562–6
104. Spragg RG, Lewis JF, Wurst W, et al. Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. *Crit Care Med* 2005; 81: 1565–61
105. Stapleton RD, Martin TR, Weiss NS, et al. A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. *Crit Care Med* 2011; 39: 1655–62
106. Staudinger T, Kofler J, Mullner M, et al. Comparison of prone positioning and continuous rotation of patients with adult respiratory distress syndrome: results of a pilot study. *Crit Care Med* 2001; 29: 51–6
107. Taccone P, Besenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009; 302: 1977–84
108. Talmon D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *JAMA* 2009; 359: 2095–104
109. Taylor RW, Zimmerman JL, Dellingr JP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA* 2004; 296: 1603–9
110. Tongyoo S, Permpikul C, Mongkolpun W, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care* 2016; 20: 329
111. Truwit JD, Bernard GR, Steingrub J, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014; 370: 2191–200
112. Tsangaris I, Galiatsou E, Kostanti N, Nakos G. The effect of exogenous surfactant in patients with lung contusions and acute lung injury. *Intensive Care Med* 2007; 33: 851
113. Varpula T, Jousela I, Niemi R, Takkunen O, Pettila V. Combined effects of prone positioning and airway pressure release ventilation on gas exchange in patients with acute lung injury. *Acta Anaesthesiol Scand* 2003; 47: 516–24
114. Varpula T, Valta P, Markkola A, et al. The effects of ventilatory mode on lung aeration assessed with computer tomography: a randomized controlled study. *J Intensive Care Med* 2009; 24: 122–30
115. Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettila V. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. *Acta Anaesthesiol Scand* 2004; 48: 722–31
116. Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Crit Care Med* 2006; 34: 1311–8
117. Vincent JL, Artigas A, Petersen LC, Meyer C. A multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial assessing safety and efficacy of active site inactivated recombinant factor VIIa.
in subjects with acute lung injury or acute respiratory distress syndrome. Crit Care Med 2009; 37: 1874–80

119. Vincent JL, Brase R, Santman F, et al. A multi-centre, double-blind, placebo-controlled study of liposomal prostaglandin E1 (TLC C-53) in patients with acute respiratory distress syndrome. Intensive Care Med 2001; 27: 1578–83

120. Voggenreiter G, Aufmkolk M, Stiletto RJ, et al. Prone positioning improves oxygenation in post-traumatic lung injury—a prospective randomized trial. J Trauma 2005; 59: 333–41. discussion 41–3

121. Weber T, Tschernich H, Sitzwohl C, et al. Tromethamine buffer modifies the depressant effect of permissive hypercapnia on myocardial contractility in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2000; 162: 1361–5

122. Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006; 354: 2213–24

123. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006; 354: 2564–75

124. Willson DF, Truwit JD, Conaway MR, Traul CS, Egan EE. The adult calfactant in acute respiratory distress syndrome trial. Chest 2015; 148: 356–64

125. Xi X-M, Jiang L, Zhu B, RM Group. Clinical efficacy and safety of recruitment maneuver in patients with acute respiratory distress syndrome using low tidal volume ventilation: a multicenter randomized controlled clinical trial. Chin Med J (Engl) 2010; 123: 3100–5

126. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. N Engl J Med 2013; 368: 806–13

127. Zeiher BG, Artigas A, Vincent JL, et al. Neutrophil elastase inhibition in acute lung injury: results of the STRIVE study. Crit Care Med 2004; 32: 1695–702

128. Zhan Q, Sun B, Liang L, et al. Early use of noninvasive positive pressure ventilation for acute lung injury. Crit Care Med 2012; 40: 455–60

129. Zhang JC, Chen XJ, Liu F, Zeng ZG, Qian KJ. Lung recruitment maneuver effects on respiratory mechanics and extravascular lung water index in patients with acute respiratory distress syndrome. World J Emerg Med 2011; 2: 201–5

130. Gao Smith F, Perkins GD, Gates S, et al. Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. Lancet 2012; 379: 229–35

131. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018; 378: 1965–75

132. Kung S-C, Hung Y-L, Chen W-L, Wang C-M, Chang H-C, Liu W-L. Effects of stepwise lung recruitment maneuvers in patients with early acute respiratory distress syndrome: a prospective, randomized, controlled trial. J Clin Med 2019; 8: 231

133. Zhen G, Shan Y, Qiao H, Wang W, Gai L, Li Z. Efficacy of Xuebijing injection in the adjunctive therapy of acute respiratory distress syndrome caused by sepsis. Int J Clin Exp Med 2019; 12: 10029–38

134. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med 2020; 382: 999–1008

135. Beitler JR, Sarge T, Banner-Goospeed VM, et al. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2019; 321: 846–57

136. Constantin J-M, Jabaudon M, Lefrant J-Y, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Med 2019; 7: 870–80

137. Fowler 3rd AA, Truwit JD, Hite RD, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomised clinical trial. JAMA 2019; 322: 1261–70

138. Frederburgh LE, Perrella MA, Barragan-Bradford D, et al. A phase I trial of low-dose inhaled carbon monoxide in sepsis-induced ARDS. JCI Insight 2018; 3, e124039

139. He H, Sun B, Liang L, et al. A multicenter RCT of noninvasive ventilation in pneumonia-induced early mild acute respiratory distress syndrome. Crit Care 2019; 23: 300

140. He J, Si X, Ji M, et al. Effect of rhubarb on extravascular lung water in patients with acute respiratory distress syndrome. Rev Assoc Med Bras (1992) 2017; 63: 435–40

141. Hodgson CL, Cooper DJ, Arabi Y, et al. Maximal recruitment open lung ventilation in acute respiratory distress syndrome (PHARLAP). A phase II, multicenter randomized controlled clinical trial. Am J Respir Crit Care Med 2019; 200: 1363–72

142. Jabaudon M, Boucher P, Imhoff E, et al. Sevoflurane for sedation in acute respiratory distress syndrome. A randomized controlled pilot study. Am J Respir Crit Care Med 2017; 195: 792–800

143. Lam NN, Hung TD, Hung DK. Impact of “opening the lung” ventilatory strategy on burn patients with acute respiratory distress syndrome. Burns 2019; 45: 1841–7

144. Li JQ, Li N, Han GJ, et al. Clinical research about airway pressure release ventilation for moderate to severe acute respiratory distress syndrome. Eur Rev Med Pharmacol Sci 2016; 20: 2634–41

145. Luo J, Wang MY, Liang BM, et al. Initial synchronized intermittent mandatory ventilation versus assist/control ventilation in treatment of moderate acute respiratory distress syndrome: a prospective randomized controlled trial. J Thorac Dis 2015; 7: 2262–73

146. Mahmoodpoor A, Hamishehkar H, Shadvar K, et al. The effect of intravenous selenium on oxidative stress in critically ill patients with acute respiratory distress syndrome. Immunol Invest 2019; 48: 147–59

147. Matthey MA, Calfee CS, Zhuo H, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. Lancet Respir Med 2019; 7: 154–62
148. Mohamed HS, Meguid MM. Effect of early continuous venous hemofiltration on E-selectin, hemodynamic stability, and ventilatory function in patients with septic-shock-induced acute respiratory distress syndrome. Biomed Res Int 2016; 2016: 7463130

149. Mohamed HS, Meguid MM. Effect of nebulized budesonide on respiratory mechanics and oxygenation in acute lung injury/acute respiratory distress syndrome: randomized controlled study. Saudi J Anaesth 2017; 11: 9–14

150. The National Heart, Lung, Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 2019; 380: 1997–2008

151. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2016; 315: 2435–41

152. Ranieri VM, Pettitá V, Karvonen MK, et al. Effect of intravenous interferon β-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: a randomized clinical trial. JAMA 2020; 323: 725–33

153. Rezaiguia-Delclaux S, Laverdure F, Genty T, et al. Neuromuscular blockade monitoring in acute respiratory distress syndrome: randomized controlled trial of clinical assessment alone or with peripheral nerve stimulation. Anesth Analg 2020. https://doi.org/10.1213/ANE.0000000000005174. Advance Access published on September 23

154. Salem MS, Elatawisy HS, Abdelhafiz AA, Alsherif S-dI. Light ultrasound- versus FiO2-guided PEEP in ARDS patients. Egypt J Anaesth 2020; 36: 31–7

155. Sobhy A, Hussiny A, Kamal M. Evaluation of the use of hypertonic saline 3% nebulizer versus intravenous hypertonic saline 3% to attenuate the manifestations of acute respiratory distress syndrome. Open Anesth J 2020; 15: 9

156. Sun R, Li Y, Chen W, Zhang F, Li T. Total ginsenosides synergize with ulinastatin against septic acute lung injury and acute respiratory distress syndrome. Int J Clin Exp Pathol 2015; 8: 7385–90

157. Tang KQ, Yang SL, Zhang B, et al. Ultrasonographic monitoring in the assessment of pulmonary recruitment and the best positive end-expiratory pressure. Medicine (Baltimore) 2017; 96: e8168

158. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 2020; 8: 267–76

159. Yu S, Hu T-X, Jin J, Zhang S. Effect of protective lung ventilation strategy combined with lung recruitment maneuver in patients with acute respiratory distress syndrome (ARDS). J Acute Dis 2017; 6: 163–8

160. Yuanbo Z, Jin W, Fei S, et al. ICU management based on PiCCO parameters reduces duration of mechanical ventilation and ICU length of stay in patients with severe thoracic trauma and acute respiratory distress syndrome. Ann Intensive Care 2016; 6: 113

161. Zheng G, Huang L, Tong H, et al. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. Respir Res 2014; 15: 39

162. Zhou Y, Jin X, Lv Y, et al. Early application of airway pressure release ventilation may reduce the duration of mechanical ventilation in acute respiratory distress syndrome. Intensive Care Med 2017; 43: 1648–59

163. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138: 720–3

164. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009; 374: 1351–63

165. Barker M, Adams S. An evaluation of a single chest physiotherapy treatment on mechanically ventilated patients with acute lung injury. Physiother Res Int 2002; 7: 157–69

166. Tamakuma S, Ogawa M, Aikawa N, et al. Relationship between neutrophil elastase and acute lung injury in humans. Pulm Pharmacol Ther 2004; 17: 271–9

167. Troncy E, Collet JP, Shapiro S, et al. Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. Am J Respir Crit Care Med 1998; 157: 1483–8

168. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c332

169. Villar J, Blanco J, del Campo R, et al. Assessment of PaO2/FiO2 for stratification of patients with moderate and severe acute respiratory distress syndrome. BMJ Open 2015; 5, e006812

170. Villar J, Fernandez RL, Ambros A, et al. A clinical classification of the acute respiratory distress syndrome for predicting outcome and guiding medical therapy. Crit Care Med 2015; 43: 346–53

171. Yehya N, Thomas NJ, Khemani RG. Risk stratification using oxygenation in the first 24 hours of pediatric acute respiratory distress syndrome. Crit Care Med 2018; 46: 619–24

172. Madotto F, Pham T, Bellani G, et al. Resolved versus persistent radiological changes in patients with acute respiratory distress syndrome after 24 h: insights from the LUNG SAFE randomised controlled trial. Intensive Care Med 2018; 44: 564–77

173. Zhang R, Wang Z, Tejera P, et al. Late-onset moderate to severe acute respiratory distress syndrome is associated with shorter survival and higher mortality: a two-stage association study. Intensive Care Med 2017; 43: 399–407

174. Lichtman SM, Harvey RD, Damiette Smit MA, et al. Modernizing clinical trial eligibility criteria: recommendations of the American society of clinical oncology-friends of cancer research organ dysfunction, prior or concurrent malignancy, and comorbidities working group. J Clin Oncol 2017; 35: 3753–9

175. Bourgeois FT, Orenstein L, Ballakur S, Mandl KD, Ioannidis JPA. Exclusion of elderly people from randomized clinical trials of drugs for ischemic heart disease. J Am Geriatr Soc 2017; 65: 2354–61

176. Laffey JG, Madotto F, Bellani G, et al. Geo-economic variation in the management of severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet Respir Med 2017; 5: 627–38

177. Rush B, McDermid RC, Celi LA, Walley KR, Russell JA, Boyd JH. Association between chronic exposure to air pollution and hospitalization for exacerbations of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Respir Crit Care Med 2017; 195: 30–9

178. Rush B, McDermid RC, Celi LA, Walley KR, Russell JA, Boyd JH. Association between chronic exposure to air pollution and hospitalization for exacerbations of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Respir Crit Care Med 2017; 195: 30–9

179. Rush B, McDermid RC, Celi LA, Walley KR, Russell JA, Boyd JH. Association between chronic exposure to air pollution and hospitalization for exacerbations of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Respir Crit Care Med 2017; 195: 30–9

180. Rush B, McDermid RC, Celi LA, Walley KR, Russell JA, Boyd JH. Association between chronic exposure to air pollution and hospitalization for exacerbations of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Respir Crit Care Med 2017; 195: 30–9

181. Rush B, McDermid RC, Celi LA, Walley KR, Russell JA, Boyd JH. Association between chronic exposure to air pollution and hospitalization for exacerbations of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Am J Respir Crit Care Med 2017; 195: 30–9
pollution and mortality in the acute respiratory distress syndrome. *Environ Pollut* 2017; **224**: 352–6

178. Ike J, Kempker J, Kramer M, Martin G. The association between acute respiratory distress syndrome mortality and annual hospital ARDS case volumes from 2002–2011 in the nationwide inpatient sample. *Am J Respir Crit Care Med* 2017; **195**: A1819

179. Laursen PN, Holmvang L, Lonborg J, et al. Unreported exclusion and sampling bias in interpretation of randomized controlled trials in patients with STEMI. *Int J Cardiol* 2019; **289**: 1–5

180. Zhang Z, Spieth PM, Chiumello D, et al. Declining mortality in patients with acute respiratory distress syndrome: an analysis of the Acute Respiratory Distress Syndrome Network trials. *Crit Care Med* 2019; **47**: 315–23

*Handling editor: Jonathan Hardman*