A systematic review of biomarkers multivariately associated with acute respiratory distress syndrome development and mortality

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Abstract

Background: Heterogeneity of acute respiratory distress syndrome (ARDS) could be reduced by identification of biomarker-based phenotypes. The set of ARDS biomarkers to prospectively define these phenotypes remains to be established.

Objective: To provide an overview of the biomarkers that were multivariately associated with ARDS development or mortality.

Data sources: We performed a systematic search in Embase, MEDLINE, Web of Science, Cochrane CENTRAL, and Google Scholar from inception until 6 March 2020.

Study selection: Studies assessing biomarkers for ARDS development in critically ill patients at risk for ARDS and mortality due to ARDS adjusted in multivariate analyses were included.

Data extraction and synthesis: We included 35 studies for ARDS development (10,667 patients at risk for ARDS) and 53 for ARDS mortality (15,344 patients with ARDS). These studies were too heterogeneous to be used in a meta-analysis, as time until outcome and the variables used in the multivariate analyses varied widely between studies. After qualitative inspection, high plasma levels of angiopoietin-2 and receptor for advanced glycation end products (RAGE) were associated with an increased risk of ARDS development. None of the biomarkers (plasma angiopoietin-2, C-reactive protein, interleukin-8, RAGE, surfactant protein D, and Von Willebrand factor) was clearly associated with mortality.

Conclusions: Biomarker data reporting and variables used in multivariate analyses differed greatly between studies. Angiopoietin-2 and RAGE in plasma were positively associated with increased risk of ARDS development. None of the biomarkers independently predicted mortality. Therefore, we suggested to structurally investigate a combination of biomarkers and clinical parameters in order to find more homogeneous ARDS phenotypes.

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**Introduction**

The acute respiratory distress syndrome (ARDS) is a major problem in the intensive care unit (ICU) with a prevalence of 10% and an in-hospital mortality rate of 40% [1, 2]. ARDS pathophysiology is based on a triad of alveolar-capillary membrane injury, high permeability alveolar oedema, and migration of inflammatory cells [3]. This triad is not routinely measured in clinical practice. Therefore, arterial hypoxemia and bilateral opacities on chest imaging following various clinical insults are used as clinical surrogates in the American European Consensus Conference (AECC) definition and the newer Berlin definition of ARDS [4, 5].

Histologically, ARDS is characterized by diffuse alveolar damage (DAD). The correlation between a clinical and histological diagnosis of ARDS is poor [6]. Only half of clinically diagnosed patients with ARDS have histological signs of DAD at autopsy [7–10]. The number of risk factors for ARDS and consequently the heterogeneous histological substrates found in patients with clinical ARDS have been recognized as a major contributor to the negative randomized controlled trial results among patients with ARDS [11].

It has been suggested that the addition of biomarkers to the clinical definition of ARDS could reduce ARDS heterogeneity by the identification of subgroups [12–15]. A retrospective latent class analysis of large randomized controlled trials identified two ARDS phenotypes largely based on ARDS biomarkers combined with clinical parameters [16, 17]. These phenotypes respond differently to the randomly assigned intervention arms. Prospective studies are required to validate these ARDS phenotypes and their response to interventions. The set of ARDS biomarkers to prospectively define these phenotypes remains to be established.

Numerous biomarkers and their pathophysiological role in ARDS have been described [12, 18]. In an earlier meta-analysis, biomarkers for ARDS development and mortality were examined in univariate analysis [19]. However, pooling of univariate biomarker data may result in overestimation of the actual effect. For this reason, we conducted a systematic review and included all biomarkers that were multivariately associated with ARDS development or mortality. This study provides a synopsis of ARDS biomarkers that could be used for future research in the identification of ARDS phenotypes.

**Methods**

This systematic review was prospectively registered in PROSPERO International Prospective Register of Systematic Reviews (PROSPERO identifier CRD42017078957) and performed according to the Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA) Statement [20]. After the search strategy, two reviewers (PZ, PS, and/or WG) separately performed study eligibility criteria, data extraction, and quality assessment. Any discrepancies were resolved by consensus, and if necessary, a third reviewer was consulted.

We searched for studies that included biomarkers that were associated with ARDS development in critically ill patients at risk for ARDS and mortality in the ARDS population in multivariate analyses adjusted for background characteristics. We did not perform a meta-analysis, because the raw data in all studies was either not transformed or log transformed resulting in varying risk ratios and confidence intervals. In addition, the majority of studies used different biomarker concentration cut-offs, resulting in varying concentration increments for risk ratios. Lastly, the number of days until mortality and variables used in multivariate analysis differed between studies. For these reasons, we limited this study to a systematic review, as the multivariate odds ratios were not comparable and pooling would result in non-informative estimates [21].

**Search strategy**

We performed a systematic search in Embase, MEDLINE, Web of Science, Cochrane CENTRAL, and Google Scholar from inception until 30 July 2018 with assistance from the Erasmus MC librarian. The search was later updated to 6 March 2020. A detailed description of the systematic search string is presented in Additional file 1. In addition, the reference lists of included studies and recent systematic reviews were screened to identify additional eligible studies.

**Study eligibility criteria**

All retrieved studies were screened on the basis of title and abstract. Studies that did not contain adult patients at risk for ARDS or with ARDS and any biomarker for ARDS were excluded. The following eligibility criteria were used: human research, adult population, studies in which biomarkers were presented as odds ratios (OR) or risk ratios in multivariate analysis with ARDS development or mortality as outcome of interest, peer-reviewed literature only, and English language. Studies comparing ARDS with healthy control subjects, case series (< 10 patients included in the study), and studies presenting gene expression fold change were excluded.

**Data extraction**

A standardized form was used for data extraction from all eligible studies. Two clinical endpoints were evaluated in this study: development of ARDS in the at-risk population (patients that did develop ARDS versus critically ill patients that did not) and mortality in the ARDS population (survivors versus non-survivors). The following data were extracted: study design and setting, study...
population, sample size, the definition of ARDS used in the study, outcome, risk ratio with 95% confidence interval in multivariate analyses, and the variables used in the analyses. In addition, the role of the biomarker in ARDS pathophysiology as reported by the studies was extracted and divided into the following categories: increased endothelial permeability, alveolar epithelial injury, oxidative injury, inflammation, pro-fibrotic, myocardial strain, coagulation, and others. Subsequently, the relative frequency distribution of biomarker roles in ARDS pathophysiology was depicted in a bar chart.

Quality assessment
Methodological quality of the included studies was assessed with the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in systematic reviews and meta-analyses [22]. Items regarding patient selection, comparability, and outcome were assessed using a descriptive approach, and a risk-of-bias score, varying between 0 (high risk) and 9 (low risk), was assigned to each study.

Results

Literature search and study selection
A total of 8125 articles were identified by the initial search and 972 by the updated search (Fig. 1). After removal of duplicates and reviewing titles and abstracts, we selected 438 articles for full-text review. A total of 86 studies was eligible for data extraction: 35 for ARDS development and 53 for ARDS mortality.

Study characteristics and quality assessment
The study characteristics of the 35 studies for ARDS development are presented in Table 1. A total of 10,667 critically ill patients was at risk for ARDS, of whom 2419 (24.6%) patients developed ARDS. The majority of

Fig. 1 PRISMA flow diagram for a systematic search
| Study          | Study design          | Study population          | ARDS definition | Outcome | Total (n) | ARDS (n) | Age (mean ± SD) | Gender, male (n (%) | Variables in multivariate analysis                                                                 | Sample moment                                      |
|---------------|-----------------------|---------------------------|-----------------|---------|-----------|-----------|----------------|-------------------|---------------------------------------------------------------------------------|--------------------------------------------------|
| Agrawal 2013  | Prospective cohort    | Critically ill            | AECC            | ALI     | 167       | 19        | 69 ± 16        | 8 (42.1%)          | APACHE II score, sepsis                                                            | Within 24 h following admission                   |
| Ahasic 2012   | Case-control          | Critically ill            | AECC            | ARDS    | 531       | 175       | 60.7 ± 17.6    | 102 (58.2%)         | Age, gender, APACHE III score, BMI, ARDS risk factor                           | Within 48 h following admission                   |
| Aisiku 2016   | RCT (TBI trial)       | Critically ill neurotrauma| Berlin          | ARDS    | 200       | 52        | 29.0 (19.5 IQR) | 50 (96.2%)         | Gender, injury severity scale, Glasgow coma scale                             | Within 24 h following injury                     |
| Amat 2000     | Case-control          | Critically ill            | AECC            | ARDS    | 35        | 21        | 54 ± 16        | 15 (71.4%)          | Not specified                                                              | At ICU admission                                 |
| Bai 2017      | Prospective cohort    | Critically ill neurotrauma| Berlin          | ARDS    | 50        | 21        | 48 (39–57 IQR) | 10 (46.7%)          | Age, gender, BMI, injury score, blood transfusion, mechanical ventilation, Marshall CT score, Glasgow coma scale | At admission                                      |
| Bai 2017      | Prospective cohort    | Critically ill trauma     | Berlin          | ARDS    | 42        | 16        | 44 (35–56 IQR) | 10 (62.5%)          | Age, gender, BMI, injury score, blood transfusion, mechanical ventilation, Marshall CT score, Glasgow coma scale | At admission                                      |
| Bai 2018      | Prospective cohort    | Stroke patients           | Berlin          | ARDS    | 384       | 60        | 64 (43–72 IQR) | 22 (36.7%)          | Age, gender, BMI, onset to treatment time, medical history                   | Within 6 h following stroke                     |
| Chen 2019     | Case-control          | Critically ill sepsis     | Berlin          | ARDS    | 115       | 57        | 56.3 ± 10.1    | 40 (70.2%)          | Age, gender, BMI, smoking history, COPD, cardiomyopathy, APACHE II score, SOFA score | Within 24 h following ARDS onset or ICU admission |
| Du 2016       | Prospective cohort    | Cardiac surgery patients  | AECC            | ALI     | 70        | 18        | 57.7 ± 11.6    | 12 (66.7%)          | Age, medical history, BMI, systolic blood pressure                            | Within 1 h following surgery                      |
| Faust 2020    | Prospective cohort    | Critically ill trauma     | Berlin          | ARDS    | 224       | 41        | 44 (30–60 IQR) | 37 (90.2%)          | Injury severity score, blunt mechanism, pre-ICU shock                        | At ED                                            |
| Faust 2020    | Prospective cohort    | Critically ill sepsis     | Berlin          | ARDS    | 120       | 45        | 62 (52–67 IQR) | 15 (33.3%)          | Lung source of sepsis, shock, age                                            | At ED                                            |
| Fremont 2010  | Case-control          | Critically ill            | AECC            | ALI/ARDS| 192       | 107       | 39 (26–53 IQR) | 71 (66.4%)          | Not specified                                                              | Within 72 h following ICU admission              |
| Gaudet 2018   | Prospective cohort    | Critically ill patients   | Berlin          | ARDS    | 72        | 11        | 56 (51–63 IQR) | 8 (72.7%)           | Not specified                                                              | At inclusion                                     |
| Hendrickson 18| Retrospective cohort  | Severe traumatic brain    | Berlin          | ARDS    | 182       | 50        | 44 ± 20       | 42 (84.0%)          | Age, acute injury scale, Glasgow coma scale, vasopressor use                  | Within 10 min following ED arrival               |
| Huang 2019    | Prospective cohort    | Critically ill sepsis     | Berlin          | ARDS    | 152       | 41        | 63.2 ± 11.0    | 32 (78.0%)          | Age, gender, BMI, smoking history, COPD, cardiomyopathy, APACHE II score,     | Within 24 h following ICU admission              |
| Study            | Study design     | Study population      | ARDS definition | Outcome Total (n) | ARDS (n) | Age | Gender, males n (%) | Variables in multivariate analysis | Sample moment |
|------------------|------------------|-----------------------|-----------------|-------------------|----------|-----|---------------------|-----------------------------------|---------------|
| Huang 2019 [36]  | Prospective cohort | Critically ill pancreatitis | Berlin ARDS    | 1933 143          | 49 (42–60 IQR) | 87 (60.8%) | Age, gender, etiology of ARDS, APACHE II score | SOFA score | At admission |
| Jabaudon 2018 [37] | Prospective cohort | Critically ill | Berlin ARDS     | 464 59            | 62 ± 16  | 46 (78.0%) | SAPS II, sepsis, shock, pneumonia |                    | Within 6 h following ICU admission |
| Jensen 2016 [38] | RCT (PASS)       | Critically ill        | Berlin ARDS     | 405 31            | NR       | NR   | Age, gender, APACHE II score, sepsis, eGFR |          | Within 24 h following admission |
| Jensen 2016 [38] | RCT (PASS)       | Critically ill        | Berlin ARDS     | 353* 31           | NR       | NR   | Age, gender, APACHE II score, sepsis, eGFR |          | Within 24 h following admission |
| Jones 2020 [39]  | Prospective cohort | Critically ill sepsis | Berlin ARDS    | 672 261           | 60 (51–69 IQR) | 154 (59.0%) | Pulmonary source, APACHE III score |          | At admission |
| Jones 2020 [39]  | Prospective cohort | Critically ill sepsis | Berlin ARDS    | 843 NR            | NR       | NR   | Pulmonary source, APACHE III score |          | Within 48 h following admission |
| Komiya 2011 [40] | Cross sectional  | Acute respiratory failure | AECC ALV/ARDS | 124 53            | 78 (69–85 IQR) | 34 (64.2%) | Age, systolic blood pressure, VEF, chest X-ray, pleural effusion |          | Within 2 h following emergency department arrival |
| Lee 2011 [41]    | Prospective cohort | Critically ill        | AECC ALV/ARDS   | 113 50            | 57.6 ± 19.1 | 24 (48.0%) | Sepsis, BMI |          | Within 24 h following ICU admission |
| Lin 2017 [42]    | Retrospective cohort | Critically ill        | Berlin ARDS    | 212 83            | 54.3 ± 20.3 | 53 (63.9%) | CRP, albumin, serum creatinine, APACHE II score |          | Within 2 h following ICU admission |
| Liu 2017 [43]    | Prospective cohort | Critically ill        | AECC ALV/ARDS   | 134 19            | 69 ± 18 | 10 (52.6%) | APACHE II, sepsis severity |          | On arrival at ED |
| Luo 2017 [44]    | Retrospective cohort | Severe pneumonia | AECC ALV/ARDS   | 157 43            | 56 ± 19 | 25 (58.1%) | Lung injury score, SOFA score, PaO2/FIO2, blood urea |          | Day 1 following admission |
| Meyer 2017 [45]  | Prospective cohort | Critically ill trauma | Berlin ARDS    | 198 100           | 60 ± 14 | 62 (62.0%) | APACHE III score, age, gender, ethnicity, pulmonary infection |          | On arrival at ED or ICU |
| Mikkelsen 2012 [46] | Case-control | Critically ill        | AECC ALV/ARDS   | 48 24             | 38 ± 20 | 22 (91.7%) | APACHE III score |          | In ED |
| Osaka 2011 [47]  | Prospective cohort | Pneumonia            | AECC ALV/ARDS   | 27 6              | 75 (51–92 range) | 4 (66.7%) | Not specified |          | 3 to 5 days following admission |
| Palashappa 2016 [48] | Prospective cohort | Critically ill        | Berlin ARDS     | 163 73            | 58 (52–68 IQR) | 42 (57.9%) | APACHE III score, diabetes, BMI, pulmonary sepsis |          | At ICU admission |
| Reilly 2018 [49] | Prospective cohort | Critically ill sepsis | Berlin ARDS     | 703 289           | 60 (51–69 IQR) | 170 (58.8%) | Pulmonary source, APACHE III score |          | Within 24 h of ICU admission |
| Shashaty 2019 [50] | Prospective cohort | Critically ill sepsis | Berlin ARDS     | 120 44            | 61 (50–68 IQR) | NR | Age, transfusion, pulmonary source, shock |          | At ED |
Table 1  Study characteristics for ARDS development (Continued)

| Study            | Study design       | Study population | ARDS definition | Outcome | ARDS (n) | Age (IQR) | Gender, male (n, %) | Variables in multivariate analysis | Sample moment |
|------------------|--------------------|------------------|----------------|---------|----------|-----------|---------------------|-----------------------------------|---------------|
| Shashaty 2019 [50] | Prospective cohort | Critically ill trauma | Berlin ARDS    | 180     | 37       | 41 (23–62 IQR) | NR | Injury severity score, blunt mechanism, transfusion | At presentation | |
| Shaver 2017 [51]  | Prospective cohort | Critically ill    | AECC ARDS      | 280     | 90       | 54 (44–64 IQR) | 54 (60.0%) | Age, APACHE II, sepsis | Day of inclusion | |
| Suzuki 2017 [52]  | Retrospective cohort | Suspected drug-induced lung injury | New bilateral lung infiltration | 68      | 39       | 72 (65–81 IQR) | 25 (64.1%) | Gender, age, smoking history, biomarkers | As soon as possible after DLI suspicion | |
| Wang 2019 [53]    | Prospective cohort | Critically ill sepsis | Berlin ARDS    | 109     | 32       | 58 ± 10.7 | NR | Age, gender, BMI, smoking history, COPD, cardiomyopathy, APACHE II score, SOFA score | Within 24 h following admission | |
| Ware 2017 [54]    | Prospective cohort | Critically ill trauma patients | Berlin ARDS    | 393     | 78       | 42 (26–55) | 56 (71.8%) | Not specified | Within 24 h following inclusion | |
| Xu 2018 [55]      | Prospective cohort | Critically ill    | Berlin ARDS    | 158     | 46       | 60.0 ± 17.1 | 35 (77.8%) | APACHE II score, Lung injury prediction score, biomarkers, sepsis | Within 24 h of ICU admission | |
| Yeh 2017 [56]     | Prospective cohort | Critically ill    | AECC ALV ARDS  | 129     | 18       | 65 ± 18   | 10 (55.6%) | APACHE II score | On arrival at the ED | |
| Ying 2019 [57]    | Prospective cohort | Critically ill pneumonia | Berlin ARDS    | 145     | 37       | 61.3 ± 10.4 | 23 (62.2%) | Age, SOFA score, lung injury score, heart rate | At admission | |

**Total**† 10,667 2419 24.6%

†Validating cohort

Some studies included patients from the same cohort

Abbreviations: AECC American European Consensus Conference definition of ARDS, ALI acute lung injury, APACHE acute physiology and chronic health evaluation, ARDS acute respiratory distress syndrome, BMI body mass index, COPD chronic obstructive pulmonary disease, CRP C-reactive protein, DLI drug-induced lung injury, ED emergency department, eGFR estimated glomerular filtration rate, ICU intensive care unit, LVEF left ventricular ejection fraction, SAPS simplified acute physiology score, SOFA sequential organ failure assessment
| Study       | Study design  | Setting       | ARDS definition | Outcome       | Total ($n$) | Non-survivors ($n$) | Age | Gender, male $n$ (%) | Variables in multivariate analysis                                                                 | Sample moment                                                                 |
|------------|---------------|---------------|-----------------|---------------|-------------|---------------------|-----|----------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Adamzik 2013 [58] | Prospective cohort | Single centre | AECC            | 30 days       | 47          | 17                  | 44 ± 13       | 32 (68.1%)          | SAPS II score, gender, lung injury score, ECOM, CVHID, BMI, CRP, procalcitonin               | Within 24 h following ICU admission                                                   |
| Ahasic 2012 [24]  | Prospective cohort | Multicentre  | AECC            | 60 days       | 175         | 78                  | 60.7 ± 17.6   | 102 (58.3%)         | Gender, BMI, cirrhosis, Diabetes, need for red cell transfusion, sepsis, Septic shock, trauma | Within 48 h following ICU admission                                                   |
| Amat 2000 [26]   | Prospective cohort | Two centre   | AECC ARDS      | 1 month after ICU discharge | 21          | 11                  | 54 ± 16        | 15 (71.4%)          | Not specified                                                   | Day 0 ICU                                                                        |
| Bajwa 2008 [59]  | Prospective cohort | Single centre | AECC            | 60 days       | 177         | 70                  | 68.3 ± 15.3   | 99 (55.9%)          | APACHE III score                                              | Within 48 h following ARDS onset                                                   |
| Bajwa 2009 [60]  | Prospective cohort | Single centre | AECC            | 60 days       | 177         | 70                  | 62.5 (IQR 29.0) | 100 (56.9%)         | APACHE III score                                              | Within 48 h following ARDS onset                                                   |
| Bajwa 2013 [61]  | RCT (FACTT)    | Multicentre   | AECC            | 60 days       | 826         | NR                  | 48 (38–59 IQR) | 442 (53.3%)         | APACHE III score                                              | Days 0 and 3                                                                    |
| Calfee 2008 [62] | RCT (ARMA)     | Multicentre   | AECC            | 180 days      | 676         | NR                  | 51 ± 17        | 282 (41.7%)         | Age, gender, APACHE III score, sepsis, or trauma                                         | Day 0                                                                            |
| Calfee 2009 [63] | RCT (ARMA)     | Multicentre   | AECC            | Hospital      | 778         | 272                 | 51 ± 17        | 459 (59.0%)         | Age, PaO$_2$/FiO$_2$, APACHE III score, sepsis or trauma                                      | Day 0                                                                            |
| Calfee 2011 [64] | RCT (ARMA)     | Multicentre   | AECC            | 90 days       | 547         | 186                 | 50 ± 16        | 227 (41.5%)         | APACHE III score, tidal volume                                   | Day 0                                                                            |
| Calfee 2012 [65] | RCT (FACTT)    | Multicentre   | AECC            | 90 days       | 931         | 261                 | 50 ± 16        | 498 (53.9%)         | Age, APACHE III score, fluid management strategy                                       | Day 0                                                                            |
| Calfee 2015 [66] | Prospective cohort | Single centre | AECC            | Hospital      | 100         | 31                  | 58 ± 11        | 52 (52.0%)          | APACHE III score                                              | Day 2 following ICU admission                                                     |
| Calfee 2015 [66] | RCT (FACTT)    | Multicentre   | AECC            | 90 days       | 853         | 259                 | 51 ± 15        | 444 (52.1%)         | APACHE III score                                              | Within 48 h following ARDS onset                                                   |
| Cartin-Ceba 2015 [67] | Prospective cohort | Single centre | AECC            | In-hospital   | 100         | 36                  | 62.5 (51–75 IQR) | 54 (54.0%)          | Acute physiology score of APACHE III score, DNR status, McCabe score                        | Within 24 h following diagnosis                                                   |
| Chen 2009 [68]   | Prospective cohort | Single centre | *              | 28 days       | 59          | 26                  | 62 ± 19        | 35 (59.3%)          | APACHE II score, biomarkers                                      | Within 24 h following diagnosis                                                   |
| Clark 1995 [69]  | Prospective cohort | Single centre | **             | Mortality     | 117         | 48                  | 43.4 ± 15.4    | 75 (64.1%)          | Lung injury score, risk factor for ARDS, lavage protein concentration                        | Day 3 following disease onset                                                    |
| Clark 2013 [70]  | RCT (FACTT)    | Multicentre   | AECC            | 60 days       | 400         | 106                 | 47 (37–57 IQR)  | 210 (52.9%)         | Age, gender, ethnicity, baseline serum creatinine, ARDS                                 | Day 1 following inclusion                                                        |
| Study          | Study design | Setting | ARDS definition | Outcome | Total (n) | Non-survivors (n) | Age | Gender, male n (%) | Variables in multivariate analysis | Sample moment |
|---------------|--------------|---------|----------------|---------|-----------|------------------|-----|-------------------|-----------------------------------|---------------|
| Dolinay 2012 [71] | Prospective cohort | Single centre | AECC | In-hospital | 28 | 17 | 54 ± 14.5 | 13 (46.4%) | APACHE II score | Within 48h following ICU admission |
| Eisner 2003 [72] | RCT (ARMA) | Multicentre | AECC | 180 days | 565 | 195 | 51 ± 17 | 332 (58.8%) | Ventilation strategy, APACHE III score, PaO2/FiO2, creatinine, platelet count | Day 0 following inclusion |
| Forel 2015 [73] | Prospective cohort | Multicentre | Berlin < 200 mmHg ICU | NR (for ICU) | 60 ± 13 | 40 (78.4%) | Lung injury score | Day 3 |
| Forel 2018 [74] | Prospective cohort | Single centre | Berlin < 200 mmHg | 60 days | 62 | 21 | 59 ± 15 | 47 (75.8%) | Gender, SOFA score, LIS score | Day 3 following onset of ARDS |
| Guervilly 2011 [75] | Prospective cohort | Single centre | AECC | 28 days | 52 | 21 | 58 ± 17 | 39 (75.0%) | Not specified | Within 24h following diagnosis |
| Kim 2019 [76] | Retrospective cohort | Single centre | Berlin In-hospital | 97 | 63 | 67.2 (64.3–70.1) | 63 (64.3%) | APACHE II score, SOFA score, SAPS II score | Within 48h following admission |
| Lee 2019 [77] | Retrospective cohort | Single centre | Berlin In-hospital | 237 | 154 | 69 (61–74 IQR) | 166 (70.0%) | Age, diabetes mellitus, non-pulmonary source, APACHE II score, SOFA | Within 24h following intubation |
| Lesur 2006 [78] | Prospective cohort | Multicentre | AECC | 28 days | 78 | 29 | 63 ± 16 | 48 (61.9%) | Age, PaCO2, APACHE II score | Within 48h following onset of ARDS |
| Li 2019 [79] | Retrospective cohort | Single centre | Berlin In-hospital | 224 | 70 | 64 (46–77 IQR) | 140 (62.9%) | APACHE II score, age, gender, BMI, smoking status, alcohol abusing status, risk factors, comorbidities | Within 24h following ICU admission |
| Lin 2010 [80] | Prospective cohort | Single centre | AECC ARDS | 28 days | 63 | 27 | 75 (57–83 IQR) | 38 (60.3%) | Age, lung injury score, SOFA score, APACHE II score, CRP, biomarkers | Within 24h following ARDS onset |
| Lin 2012 [81] | Prospective cohort | Single centre | AECC | 30 days | 87 | 27 | 61 (56–70 IQR) | 42 (48.3%) | APACHE II, Lung injury score, creatinine, biomarkers | At inclusion |
| Lin 2013 [82] | Prospective cohort | Single centre | AECC | 30 days | 78 | 22 | 63 (54–68 IQR) | 45 (57.7%) | Age, APACHE II score, Lung injury score, PaO2/FiO2 | Within 10h following diagnosis |
| Madtes 1998 [83] | Prospective cohort | Single centre | *** | In-hospital | 74 | 33 | 38 (19–68 Range) | 50 (67.6%) | Age, PCP III levels, neutrophils, lung injury score | Day 3 following ARDS onset |
| McClintock 2006 [84] | RCT (ARMA) | Multicentre | AECC | Mortality | 579 | NR | 51 ± 17 | 333 (57.9%) | Ventilator group assignment | Day 0 following inclusion |
| McClintock 2007 [85] | RCT (ARMA) | Multicentre | AECC | Mortality | 576 | NR | 52 ± 17 | 328 (56.9%) | Gender, ventilator group assignment, eGFR, age, APACHE III score, | Day 0 following inclusion |
| Study          | Study design   | Setting          | ARDS definition | Outcome   | Total (n) | Non-survivors (n) | Age         | Variables in multivariate analysis                                                                                      | Sample moment     |
|--------------|---------------|-----------------|-----------------|-----------|-----------|-------------------|-------------|------------------------------------------------------------------------------------------------------------------------|-------------------|
| McClintock 2008 [86] | Prospective cohort | Two centre | AECC           | In-hospital | 50        | 21                | 55 ± 16     | Age, gender, SAPS II, vasopressor use, sepsis                                                                         | Within 48 h following diagnosis |
| Menk 2018 [87] | Retrospective cohort | Single centre | Berlin         | ICU       | 404       | 182               | 50 (37–61 IQR)| Age, gender, APACHE II score, SOFA, severe ARDS, peak airway pressure, pulmonary compliance | Within 24 h following admission |
| Metkus 2017 [88] | RCT (ALVEOLI, FACTT) | Multicentre | AECC           | 60 days    | 1057      | NR                | 504         | Age, gender, trial group assignment                                                                                  | Within 24 h following inclusion |
| Mrozek 2016 [89] | Prospective cohort | Multicentre | AECC           | 90 days    | 119       | 42                | 57 ± 17     | Age, gender, SAPS II score, PaO₂/FiO₂, sepsis                                                                         | Within 24 h following inclusion |
| Ong 2010 [90]  | Prospective cohort | Two centre | AECC           | 28-day in-hospital | 24       | NR                | 51 ± 21     | Age, gender, PaO₂/FiO₂, tidal volume, plateau pressure, APACHE II score                                              | At inclusion       |
| Parsons 2005 [91] | RCT (ARMA) | Multicentre | AECC           | 180 days or discharge | 562      | 196               | NR          | Ventilation strategy, APACHE III score, PaO₂/FiO₂, creatinine, plateau count, vasopressor use | At inclusion       |
| Parsons 2005 [92] | RCT (ARMA) | Multicentre | AECC           | In-hospital | 781       | 276               | 516 ± 17.3  | Ventilation strategy, APACHE III score, PaO₂/FiO₂, creatinine, plateau count, vasopressor use | Day 0             |
| Quesnel 2012 [93] | Prospective cohort | Single centre | AECC           | 28 days    | 92        | 37                | 67 (49–74 IQR)| Age, SAPS II score, malignancy, SOFA score, BAL characteristics                                                        | NR                |
| Rahmel 2018 [94] | Retrospective cohort | Single centre | AECC           | 30 days    | 119       | 37                | 43.7 ± 13.3 | Age, SOFA score                                                                                                        | Within 24 h following admission |
| Reddy 2019 [95] | Prospective cohort | Single centre | Berlin         | 30 days    | 39        | 19                | 55 (47.5–61.5)| Not specified                                                                                                         | Within 24 h of ARDS diagnosis |
| Rivara 2012 [96] | Prospective cohort | Single centre | AECC           | 60 days    | 177       | 70                | 71.5 (59–80 IQR)| APACHE III score                                                                                                      | Within 48 h following diagnosis |
| Rogers 2019 [97] | RCT (SAILS) | Multicentre | AECC           | 60 days    | 683       | NR                | 56 (43–65)  | Age, race, APACHE III score, GFR, randomization, shock                                                                 | Within 48 h following ARDS diagnosis |
| Sapru 2015 [98]  | RCT (FACTT) | Multicentre | AECC           | 60 days    | 449       | 109               | 498 ± 15.6  | Age, gender, APACHE III score, pulmonary sepsis, fluid management strategy                                           | Upon inclusion     |
| Suratt 2009 [99] | RCT (ARMA) | Multicentre | AECC           | In-hospital | 645       | 222               | 51 ± 17     | Ventilation strategy                                                                                                 | Day 0             |
| Study          | Study design | Setting       | ARDS definition | Outcome | Total (n) | Non-survivors (n) | Age            | Gender, male (n) | Variables in multivariate analysis | Sample moment |
|---------------|--------------|---------------|-----------------|---------|-----------|------------------|----------------|-----------------|-----------------------------------|---------------|
| Tang 2014 [100] | Prospective cohort | Multicentre Berlin | In-hospital | 42      | 20        | 72.5 ± 10.8      | (59.1%)        | 27 (64.3%) | APACHE II score, PaO2/FIO2, CRP, WBC, procalcitonin | Within 24h following diagnosis |
| Tsangaris 2009 [101] | Prospective cohort | Single centre AECC | 28 days       | 52      | 27        | 66.1 ± 16.9      | (59.6%)        | 32 (64.4%) | APACHE II score, age, genotype | Within 48h following admission |
| Tsangaris 2017 [102] | Prospective cohort | Single centre NR | 28 days       | 53      | 28        | 64.6 ± 16.8      | (62.3%)        | 33 (62.3%) | Lung injury score | Within 48h following diagnosis |
| Tsantes 2013 [103] | Prospective cohort | Single centre AECC | 28 days       | 69      | 34        | 64.4 ± 17.9      | (62.3%)        | 43 (62.3%) | Age, gender, APACHE II score, SOFA score, pulmonary parameters, serum lactate | Within 48h following diagnosis |
| Tseng 2014 [104] | Prospective cohort | Single centre AECC ARDS ICU | 56      | 16        | 70.6 ± 9.2     | (55.4%)        | 31 (55.4%) | APACHE II score, SOFA score, SAPS II score | Day 1 following ICU admission |
| Wang 2017 [105]  | Prospective cohort | Multicentre Berlin | 60 days       | 167     | 62        | 76.5 (19–95 range) | (67.1%)        | 112 (67.1%) | Age, gender, APACHE II score | Day 1 following diagnosis |
| Wang 2018 [106]  | Retrospective cohort | Single centre AECC | Mortality | 247     | 146      | 62 (48–73 IQR)  | (65.6%)        | 162 (65.6%) | Age, creatinine, PaO2/FIO2 | Within 24h following diagnosis |
| Ware 2004 [107]  | RCT (ARMA) | Multicentre AECC | In-hospital | 559     | 193      | 51 ± 17           | (59.8%)        | 332 (59.4%) | Ventilator strategy, APACHE III score, PaO2/FIO2, creatinine, platelet count | Day 0 of inclusion |
| Xu 2017 [108]   | Retrospective cohort | Single centre Berlin | 28 days       | 63      | 27        | 54 (42–67 IQR)  | (58.7%)        | 37 (58.7%) | APACHE II score, PaO2/FIO2, procalcitonin | Within 48 following admission |
| **Total**       |               |               |                 | 15,344  | 3914      |                 | 36.0%          |                 |                                    |               |

*Respiratory failure requiring positive pressure ventilation, PF ratio < 200 mmHg, bilateral pulmonary infiltration on chest X-ray, no clinical evidence of left atrial hypertension
**PF ratio < 150 mmHg, PF < 200 mmHg with 5 PEEP, diffuse parenchymal infiltrates, pulmonary artery wedge pressure < 18 mmHg, no clinical evidence of congestive heart failure
***PF ratio < 150 mmHg, PF ratio < 200 mmHg with 5 cmH2O PEEP, diffuse parenchymal infiltrates, pulmonary artery wedge pressure < 18 mmHg, or no clinical evidence of congestive heart failure
†Some studies included patients from the same cohort

Abbreviations: AECC American European Consensus Conference definition of ARDS, APACHE acute physiology and chronic health evaluation, ARDS acute respiratory distress syndrome, BAL bronchoalveolar lavage, BMI body mass index, CRP C-reactive protein, CVVHD continuous veno-venous haemodialysis, DNR do not resuscitate, ECMO extra corporeal membrane oxygenation, eGFR estimated glomerular filtration rate, FIO2 fraction of inspired oxygen, ICU intensive care unit, PCP procollagen, No. number, SAPS simplified acute physiology score, SOFA sequential organ failure assessment, WBC white blood cell count
Table 3  Risk ratios for ARDS development in the at-risk population

| Biomarkers in plasma | Reference | Biomarker role in ARDS | Sample size | Risk ratio (95% CI) | Cut-off | Comment |
|----------------------|-----------|------------------------|-------------|---------------------|---------|---------|
| Adiponectin          | Palakshappa 2016 [48] | Anti-inflammatory | 163 | 1.12 (1.01–1.25) | Per 5 mcg/mL | |
| Angiopoietin-2       | Agrawal 2013 [23] | Increased endothelial permeability | 167 | 1.8 (1.0–3.4) | Per log10 | |
| Angiopoietin-2       | Fremont 2010 [32] | Increased endothelial permeability | 192 | 2.20 (1.19–4.05) | Highest vs lowest quartile | |
| Angiopoietin-2       | Reilly 2018 [49] | Increased endothelial permeability | 703 | 1.49 (1.20–1.77) | Per log increase | |
| Angiopoietin-2       | Ware 2017 [54] | Increased endothelial permeability | 393 | 1.890 (1.322–2.702) | 1st vs 4th quartile | |
| Angiopoietin-2       | Xu 2018 [55] | Increased endothelial permeability | 158 | 1.258 (1.137–1.392) | |
| Advanced oxidant protein products | Du 2016 [30] | Oxidative injury | 70 | 1.164 (1.068–1.269) | |
| Brain natriuretic peptide | Fremont 2010 [32] | Myocardial strain | 192 | 0.45 (0.26–0.77) | Highest vs lowest quartile | |
| Brain natriuretic peptide | Komiya 2011 [40] | Myocardial strain | 124 | 14.425 (4.382–47.483) | > 500 pg/mL | Outcome is CPE |
| Club cell secretory protein | Jensen 2016 [38] | Alveolar epithelial injury | 405 | 2.6 (0.7–9.7) | ≥ 42.8 ng/mL | Learning cohort |
| Club cell secretory protein | Jensen 2016 [38] | Alveolar epithelial injury | 353 | 0.96 (0.20–4.5) | ≥ 42.8 ng/mL | Validating cohort |
| Club cell secretory protein | Lin 2017 [42] | Alveolar epithelial injury | 212 | 1.096 (1.085–1.162) | |
| C-reactive protein (CRP) | Bai 2018 [28] | Inflammation | 384 | 1.314 (0.620–2.603) | |
| C-reactive protein (CRP) | Chen 2019 [29] | Inflammation | 115 | 0.994 (0.978–1.010) | |
| C-reactive protein (CRP) | Huang 2019 [35] | Inflammation | 152 | 1.287 (0.295–5.606) | ≥ 90.3 mg/L | |
| C-reactive protein (CRP) | Huang 2019 [36] | Inflammation | 1933 | 1.008 (1.007–1.010) | |
| C-reactive protein (CRP) | Komiya 2011 [40] | Inflammation | 124 | 0.106 (0.035–0.323) | > 50 mg/L | Outcome is CPE |
| C-reactive protein (CRP) | Lin 2017 [42] | Inflammation | 212 | 1.007 (1.001–1.014) | |
| C-reactive protein (CRP) | Osaka 2011 [47] | Inflammation | 27 | 1.029 (0.829–1.293) | Per 1 mg/dL increase | |
| C-reactive protein (CRP) | Wang 2019 [53] | Inflammation | 109 | 1.000 (0.992–1.008) | |
| C-reactive protein (CRP) | Ying 2019 [57] | Inflammation | 145 | 1.22 (0.95–1.68) | |
| Free 2-chlorofatty acid | Meyer 2017 [45] | Oxidative injury | 198 | 1.62 (1.25–2.09) | Per log10 | |
| Total 2-chlorofatty acid | Meyer 2017 [45] | Oxidative injury | 198 | 1.82 (1.32–2.52) | Per log10 | |
| Free 2-chlorostearic acid | Meyer 2017 [45] | Oxidative injury | 198 | 1.82 (1.41–2.37) | Per log10 | |
| Total 2-chlorostearic acid | Meyer 2017 [45] | Oxidative injury | 198 | 1.78 (1.31–2.43) | Per log10 | |
| Endocan | Gaudet 2018 [33] | Leukocyte adhesion inhibition | 72 | 0.001 (0–0.215) | > 5.36 ng/mL | |
| Reference                  | Biomarker role in ARDS                                           | Sample size | Risk ratio (95% CI) | Cut-off          | Comment                      |
|----------------------------|----------------------------------------------------------------|-------------|---------------------|------------------|------------------------------|
| Endocan Mikkelsen 2012    | Leukocyte adhesion inhibition                                   | 48          | 0.69 (0.49–0.97)    |                  | 1 unit increase              |
| Endocan Ying 2019         | Leukocyte adhesion modulation                                   | 145         | 1.57 (1.14–2.25)    |                  |                              |
| Fibrinogen Luo 2017       | Coagulation                                                     | 157         | 1.893 (1.141–3.142) |                  |                              |
| Glutamate Bai 2017        | Non-essential amino acid, neurotransmitter                     | 50          | 2.229 (1.082–2.634) |                  |                              |
| Glutamate Bai 2017        | Non-essential amino acid, neurotransmitter                     | 42          | 0.996 (0.965–1.028) |                  |                              |
| Glutamate Bai 2018        | Non-essential amino acid                                        | 384         | 3.022 (2.001–4.043) |                  |                              |
| Growth arrest-specific gene 6 | Endothelial activation                                        | 129         | 1.6 (1.3–2.6)       |                  |                              |
| Insulin-like growth factor 1 | Ahasic 2012 Pro-fibrotic                                         | 531         | 0.58 (0.42–0.79)    | Per log10        |                              |
| IGF binding protein 3     | Ahasic 2012 Pro-fibrotic                                         | 531         | 0.57 (0.40–0.81)    | Per log10        |                              |
| Interleukin-1 beta        | Aisiku 2016 Pro-inflammatory                                    | 194         | 0.98 (0.73–1.32)    |                  |                              |
| Interleukin-1 beta        | Chen 2019 Anti-inflammatory                                     | 115         | 1.001 (0.945–1.061) |                  |                              |
| Interleukin-1 beta        | Huang 2019 Pro-inflammatory                                    | 152         | 0.666 (0.152–2.910) | ≥ 11.3 pg/mL      |                              |
| Interleukin-1 beta        | Wang 2019 Pro-inflammatory                                     | 109         | 1.021 (0.982–1.063) |                  |                              |
| Interleukin-6             | Aisiku 2016 Pro-inflammatory                                    | 195         | 1.24 (1.05–1.49)    |                  |                              |
| Interleukin-6             | Bai 2018 Pro-inflammatory                                       | 384         | 1.194 (0.806–1.364) |                  |                              |
| Interleukin-6             | Chen 2019 Anti-inflammatory                                     | 115         | 0.998 (0.993–1.003) |                  |                              |
| Interleukin-6             | Huang 2019 Pro-inflammatory                                    | 152         | 0.512 (0.156–1.678) | ≥ 63.7 pg/mL      |                              |
| Interleukin-6             | Yeh 2017 Pro-inflammatory                                       | 129         | 1.4 (0.98–1.7)      |                  |                              |
| Interleukin-8             | Agrawal 2013 Pro-inflammatory                                   | 167         | 1.3 (0.97–1.8)      | Per log10        |                              |
| Interleukin-8             | Aisiku 2016 Pro-inflammatory                                    | 194         | 1.26 (1.04–1.53)    |                  |                              |
| Interleukin-8             | Chen 2019 Anti-inflammatory                                     | 115         | 1.000 (0.996–1.003) |                  |                              |
| Interleukin-8             | Fremont 2010 Anti-inflammatory                                  | 192         | 1.81 (1.03–3.17)    | Highest vs lowest quartile |                              |
| Interleukin-8             | Liu 2017 Anti-inflammatory                                      | 134         | 1.4 (0.98–1.7)      | Per log10        |                              |
| Interleukin-8             | Yeh 2017 Pro-inflammatory                                       | 129         | 1.4 (0.92–1.7)      |                  |                              |
| Interleukin-10            | Aisiku 2016 Anti-inflammatory                                   | 195         | 1.66 (1.22–2.26)    |                  |                              |
| Interleukin-10            | Chen 2019 Anti-inflammatory                                     | 115         | 1.003 (0.998–1.018) |                  |                              |
| Interleukin-10            | Fremont 2010 Anti-inflammatory                                  | 192         | 2.02                  | Highest vs lowest |                              |
| Reference | Biomarker role in ARDS | Sample size | Risk ratio (95% CI) | Cut-off | Comment |
|-----------|------------------------|-------------|----------------------|---------|---------|
| Interleukin-12p70 | Aisiku 2016 [25] | Pro-inflammatory | 194 | 1.18 (0.82–1.69) | quartile |
| Interleukin-17 | Chen 2019 [29] | Pro-inflammatory | 115 | 1.003 (1.000–1.007) | Not significant |
| Interleukin-17 | Huang 2019 [35] | Pro-inflammatory | 152 | 0.644 (0.173–2.405) | ≥ 144.55 pg/mL |
| Interleukin-17 | Wang 2019 [53] | Pro-inflammatory | 109 | 1.001 (0.997–1.004) | |
| Leukotriene B4 | Amat 2000 [26] | Pro-inflammatory | 52 | 14.3 (2.3–88.8) | > 14 pmol/mL |
| Microparticles | Shaver 2017 [51] | Coagulation | 280 | 0.693 (0.490–0.980) | Per 10 μM |
| Mitochondrial DNA | Faust 2020 [31] | Damage-associated molecular pattern | 224 | 1.18 (1.14–2.19) | 48 h plasma |
| Mitochondrial DNA | Faust 2020 [31] | Damage-associated molecular pattern | 120 | 1.52 (1.12–2.06) | Per log copies per microlitre |
| Myeloperoxidase | Meyer 2017 [45] | Pro-inflammatory | 198 | 1.28 (0.89–1.84) | Per log10 |
| Nitric oxide | Aisiku 2016 [25] | Oxidative injury | 193 | 1.60 (0.98–2.90) | |
| Parkinson disease 7 | Liu 2017 [43] | Anti-oxidative injury | 134 | 1.8 (1.1–3.5) | Per log10 |
| Pre B cell colony enhancing factor | Lee 2011 [41] | Pro-inflammatory | 113 | 0.78 (0.43–1.41) | Per 10 fold increase |
| Procalcitonin | Bai 2018 [28] | Inflammation | 384 | 1.156 (0.844–1.533) | |
| Procalcitonin | Chen 2019 [29] | Inflammation | 115 | 1.020 (0.966–1.077) | |
| Procalcitonin | Huang 2019 [35] | Inflammation | 152 | 2.506 (0.705–8.913) | ≥ 13.2 ng/mL |
| Procalcitonin | Huang 2019 [36] | Inflammation | 1933 | 1.008 (1.000–1.016) | Not significant |
| Procalcitonin | Wang 2019 [53] | Inflammation | 109 | 1.019 (0.981–1.058) | European ancestry |
| Procollagen III | Fremont 2010 [32] | Pro-fibrotic | 192 | 2.90 (1.61–5.23) | Highest vs lowest quartile |
| Receptor for advanced glycation end products | Fremont 2010 [32] | Alveolar epithelial injury | 192 | 3.33 (1.85–5.99) | Highest vs lowest quartile |
| Receptor for advanced glycation end products | Jabaudon 2018 [37] | Alveolar epithelial injury | 464 | 2.25 (1.50–3.16) | Per log10 |
| Receptor for advanced glycation end products | Jabaudon 2018 [37] | Alveolar epithelial injury | 464 | 4.33 (2.85–6.56) | Per log10 |
| Receptor for advanced glycation end products | Jones 2020 [39] | Alveolar epithelial injury | 672 | 1.73 (1.35–2.21) | European ancestry |
| Receptor for advanced glycation end products | Jones 2020 [39] | Alveolar epithelial injury | 672 | 2.05 (1.50–2.83) | African ancestry |
| Receptor for advanced glycation end products | Jones 2020 [39] | Alveolar epithelial injury | 843 | 2.56 (2.14–3.06) | European ancestry |
| Receptor for advanced glycation end products | Ware 2017 [54] | Alveolar epithelial injury | 393 | 2.382 (1.638–3.464) | 1st vs 4th quartile |
| Receptor interacting protein kinase-3 | Shashaty 2019 [50] | Increased endothelial permeability | 120 | 1.30 (1.03–1.63) | Per 0.5 SD |
studies used the Berlin definition of ARDS (21/35), followed by the AECC criteria of ARDS (13/35). The included biomarkers were measured in plasma, cerebrospinal fluid, and bronchoalveolar lavage fluid. In all studies, the first sample was taken within 72 h following ICU admission.

The study characteristics of the 53 studies for ARDS mortality are presented in Table 2. A total of 15,344 patients with ARDS were included with an observed mortality rate of 36.0%. The AECC definition of ARDS was used in the majority of included studies (39/53). The included biomarkers were measured in plasma, bronchoalveolar lavage fluid, and urine. All samples were taken within 72 h following the development of ARDS.

The median quality of the included publications according to the NOS was 7 (range 4–9) for ARDS.
development and 8 (range 5–9) for ARDS mortality (Additional file 2).

Biomarkers associated with ARDS development in the at-risk population
A total of 37 biomarkers in plasma, 7 in cerebrospinal fluid, and 1 in bronchoalveolar lavage fluid were assessed in multivariate analyses (Table 3). Five studies examined angiopoietin-2 (Ang-2) and seven studies examined receptor for advanced glycation end products (RAGE). In all studies, high plasma levels of Ang-2 and RAGE were significantly associated with an increased risk of ARDS development in the at-risk population. Similar results were seen for surfactant protein D (SpD) in plasma in all three studies that assessed SpD. In contrast, biomarkers for inflammation as C-reactive protein (CRP), procalcitonin, interleukin-6, and interleukin-8 were not clearly associated with ARDS development. The majority of biomarkers in plasma are surrogates for inflammation in ARDS pathophysiology (Fig. 2).

Biomarkers associated with mortality in the ARDS population
A total of 49 biomarkers in plasma, 8 in bronchoalveolar lavage fluid, and 3 in urine were included in this study (Table 4). Ang-2, CRP, interleukin-8 (IL-8), RAGE, SpD, and Von Willebrand factor (VWF) in plasma were assessed in four or more studies. However, none of these biomarkers was associated with ARDS mortality in all four studies. Similarly to biomarkers in ARDS development, the majority of biomarkers for ARDS mortality in plasma had a pathophysiological role in inflammation (Fig. 2). The majority of biomarkers measured in bronchoalveolar lavage fluid had a pro-fibrotic role in ARDS pathophysiology.

Discussion
In the current systematic review, we present a synopsis of biomarkers for ARDS development and mortality tested in multivariate analyses. We did not perform a meta-analysis because of severe data heterogeneity between studies. Upon qualitative inspection, we found that high levels of Ang-2 and RAGE were associated with ARDS development in the at-risk population. None of the biomarkers assessed in four or more studies was associated with an increased mortality rate in all studies. The majority of plasma biomarkers for both ARDS development and mortality are surrogates for inflammation in ARDS pathophysiology.

Previously, Terpstra et al. [19] calculated univariate ORs from absolute biomarker concentrations and performed a meta-analysis. They found that 12 biomarkers in plasma were associated with mortality in patients with ARDS. However, a major limitation of their meta-analysis is that these biomarkers were tested in univariate analyses without considering confounders as disease severity scores. Given the high univariate ORs as compared to the multivariate ORs found in this systematic review, the performance of these biomarkers is likely to be overestimated. Jabaudon et al. [109] found in an individual patient data meta-analysis that high concentrations of plasma RAGE were associated with 90-day mortality independent of driving pressure or tidal volume. However, they could not correct for disease severity score as these differed between studies. Unfortunately, we were unable to perform a meta-analysis on...
Table 4 Risk ratios for ARDS mortality in the ARDS population

| Biomarkers in plasma | Reference | Biomarker role in ARDS | Sample size | Risk ratio (95% CI) | Cut-off | Comment |
|----------------------|-----------|------------------------|-------------|---------------------|---------|---------|
| Activin-A            | Kim 2019 [76] | Pro-fibrotic | 97          | 2.64 (1.04–6.70)   |         |         |
| Angiopoietin-1/angiopoietin-2 ratio | Ong 2010 [90] | Modulates endothelial permeability | 24          | 5.52 (1.22–24.9)   |         |         |
| Angiopoietin-2       | Calfee 2012 [65] | Increased endothelial permeability | 931         | 0.92 (0.73–1.16)   | Per log10 | Infection-related ALI |
| Angiopoietin-2       | Calfee 2012 [65] | Increased endothelial permeability | 931         | 1.94 (1.15–3.25)   | Per log10 | Noninfection-related ALI |
| Angiopoietin-2       | Calfee 2015 [66] | Increased endothelial permeability | 100         | 2.54 (1.38–4.68)   | Per log10 | Single centre |
| Angiopoietin-2       | Calfee 2015 [66] | Increased endothelial permeability | 853         | 1.43 (1.19–1.73)   | Per log10 | Multicentre |
| Angiotensin 1–9      | Reddy 2019 [95] | Pro-fibrotic | 39          | 2.24 (1.15–4.39)   | Concentration doubled (in Ln) |         |
| Angiotensin 1–10     | Reddy 2019 [95] | Pro-fibrotic | 39          | 0.36 (0.18–0.72)   | Concentration doubled (in Ln) |         |
| Angiotensin converting enzyme | Tsantes 2013 [103] | Endothelial permeability, pro-fibrotic | 69          | 1.06 (1.02–1.10)   | Per 1 unit increase | 28-day mortality |
| Angiotensin converting enzyme | Tsantes 2013 [103] | Endothelial permeability, pro-fibrotic | 69          | 1.04 (1.01–1.07)   | Per 1 unit increase | 90-day mortality |
| NT-pro brain natriuretic peptide | Bajwa 2008 [59] | Myocardial strain | 177         | 2.36 (1.11–4.99)   | ≥ 6813 ng/L |         |
| NT-pro brain natriuretic peptide | Lin 2012 [81] | Myocardial strain | 87          | 2.18 (1.54–4.46)   | Per unit |         |
| Club cell secretory protein | Cartin-Ceba 2015 [67] | Alveolar epithelial injury | 100         | 1.09 (0.60–2.02)   | Per log10 |         |
| Club cell secretory protein | Lesur 2006 [78] | Alveolar epithelial injury | 78          | 1.37 (1.25–1.83)   | Increments of 0.5 |         |
| Copeptin             | Lin 2012 [81] | Osmo-regulatory | 87          | 4.72 (2.48–7.16)   | Per unit |         |
| C-reactive protein (CRP) | Adamzik 2013 [58] | Inflammation | 47          | 1.01 (0.9–1.1)     | Per log10 |         |
| C-reactive protein (CRP) | Bajwa 2009 [60] | Inflammation | 177         | 0.67 (0.52–0.87)   | Per log10 |         |
| C-reactive protein (CRP) | Lin 2010 [80] | Inflammation | 63          | 2.316 (0.652–8.226) |         |         |
| C-reactive protein (CRP) | Tseng 2014 [104] | Inflammation | 56          | 1.265 (0.798–2.005) | Day 3 |         |
| D-dimer              | Tseng 2014 [104] | Coagulation | 56          | 1.211 (0.818–1.793) | Validation cohort |         |
| Decoy receptor 3     | Chen 2009 [68] | Immunomodulation | 59          | 4.02 (1.20–13.52)  | > 1 ng/mL |         |
| Endocan              | Tang 2014 [100] | Leukocyte adhesion inhibition | 42          | 1.374 (1.150–1.641) | > 4.96 ng/mL |         |
| Endocan              | Tsangaris 2017 [102] | Leukocyte adhesion inhibition | 53          | 3.36 (0.74–15.31)  | > 13 ng/mL |         |
| Galectin 3           | Xu 2017 [108] | Pro-fibrotic | 63          | 1.002 (0.978–1.029) | Per 1 ng/mL |         |
| Granulocyte colony stimulating factor | Suratt 2009 [99] | Inflammation | 645         | 1.70 (1.06–2.75)   | Quartile 4 vs quartile 2 |         |
| Growth differentiation factor-15 | Clark 2013 [70] | Pro-fibrotic | 400         | 2.86 (1.84–4.54)   | Per log10 |         |
| Reference            | Biomarker role in ARDS                      | Sample size | Risk ratio (95% CI) | Cut-off          | Comment                  |
|----------------------|-----------------------------------------------|-------------|---------------------|-------------------|--------------------------|
| Heparin binding protein Lin 2013 [82] | Inflammation, endothelial permeability       | 78          | 1.52 (1.12–2.85)    | Per log10         |                          |
| High mobility group protein B1 Tseng 2014 [104] | Pro-inflammatory                            | 56          | 1.002 (1.000–1.004) |                   | Day 1                    |
| High mobility group protein B1 Tseng 2014 [104] | Pro-inflammatory                            | 56          | 0.990 (0.968–1.013) |                   | Day 3                    |
| Insulin-like growth factor Ahasic 2012 [24]      | Pro-fibrotic                                 | 175         | 0.70 (0.51–0.95)    | Per log10         |                          |
| IGF binding protein 3 Ahasic 2012 [24]           | Pro-fibrotic                                 | 175         | 0.69 (0.50–0.94)    | Per log10         |                          |
| Intercellular adhesion molecule-1 Calfee 2009 [63] | Pro-inflammatory                            | 778         | 1.22 (0.99–1.49)    | Per log10         |                          |
| Intercellular adhesion molecule-1 Calfee 2011 [64] | Pro-inflammatory                            | 547         | 0.74 (0.59–0.95)    | Per natural log   |                          |
| Intercellular adhesion molecule-1 McClintock 2008 [86] | Pro-inflammatory                            | 50          | 5.8 (1.1–30.0)      | Per natural log   |                          |
| Interleukin-1 beta Lin 2010 [80]                 | Pro-inflammatory                             | 63          | 1.355 (0.357–5.140) | Per log 10        |                          |
| Interleukin-6 Calfee 2015 [66]                   | Pro-inflammatory                             | 100         | 1.81 (1.34–2.45)    | Per log10         | Single centre            |
| Interleukin-6 Calfee 2015 [66]                   | Pro-inflammatory                             | 853         | 1.24 (1.14–1.35)    | Per log10         | Multicentre              |
| Interleukin-6 Parsons 2005 [92]                  | Pro-inflammatory                             | 781         | 1.18 (0.93–1.49)    | Per log10         |                          |
| Interleukin-8 Amat 2000 [26]                     | Pro-inflammatory                             | 21          | 0.09 (0.01–1.35)    | > 150 pg/mL       |                          |
| Interleukin-8 Calfee 2011 [64]                   | Pro-inflammatory                             | 547         | 1.36 (1.15–1.62)    | Per natural log   |                          |
| Interleukin-8 Calfee 2015 [66]                   | Pro-inflammatory                             | 100         | 1.65 (1.25–2.17)    | Per log10         | Single centre            |
| Interleukin-8 Calfee 2015 [66]                   | Pro-inflammatory                             | 853         | 1.41 (1.27–1.57)    | Per log10         | Multicentre              |
| Interleukin-8 Cartin-Ceba 2015 [67]              | Pro-inflammatory                             | 100         | 1.08 (0.72–1.61)    | Per log10         |                          |
| Interleukin-8 Lin 2010 [80]                      | Pro-inflammatory                             | 63          | 0.935 (0.280–3.114) | Per log 10        |                          |
| Interleukin-8 McClintock 2008 [86]               | Pro-inflammatory                             | 50          | 2.0 (1.1–4.0)       | Per natural log   |                          |
| Interleukin-8 Parsons 2005 [92]                  | Pro-inflammatory                             | 780         | 1.73 (1.28–2.34)    | Per log10         |                          |
| Interleukin-8 Tseng 2014 [104]                   | Pro-inflammatory                             | 56          | 1.039 (0.955–1.130) |                   | Day 1                    |
| Interleukin-8 Tseng 2014 [104]                   | Pro-inflammatory                             | 56          | 1.075 (0.940–1.229) |                   | Day 3                    |
| Interleukin-10 Parsons 2005 [92]                 | Anti-inflammatory                            | 593         | 1.23 (0.86–1.76)    | Per log10         |                          |
| Interleukin-18 Dolinay 2012 [71]                 | Pro-inflammatory                             | 28          | 1.60 (1.17–2.20)    | Per 500 pg/mL     | increase                |
| Interleukin-18 Rogers 2019 [97]                  | Pro-inflammatory                             | 683         | 2.2 (1.5–3.1)       | ≥ 800 pg/mL       |                          |
| Leukocyte microparticles Guervilly 2011 [75]     | Immunomodulation                             | 52          | 5.26 (1.10–24.99)   | < 60 elements/μL  |                          |
| Leukotriene B4 Amat 2000                         | Pro-inflammatory                             | 21          | 22.5                | > 14 pmol/mL      |                          |
| Reference | Biomarker role in ARDS | Sample size | Risk ratio (95% CI) | Cut-off | Comment |
|-----------|-----------------------|-------------|---------------------|---------|---------|
| Neutrophil elastase Wang 2017 [105] | Pro-inflammatory | 167 | 1.76 (p value 0.002) | 1 SD change | Day 1 |
| Neutrophil elastase Wang 2017 [105] | Pro-inflammatory | 167 | 1.58 (p value 0.06) | 1 SD change | Day 3 |
| Neutrophil elastase Wang 2017 [105] | Pro-inflammatory | 167 | 1.70 (p value 0.001) | 1 SD change | Day 7 |
| Neutrophil to lymphocyte ratio Li 2019 [79] | Pro-inflammatory | 224 | 5.815 (1.824–18.533) | First–fourth quartile | |
| Neutrophil to lymphocyte ratio Wang 2017 [105] | Pro-inflammatory | 167 | 1.58 (p value 0.06) | 1 SD change | Day 3 |
| Neutrophil to lymphocyte ratio Wang 2017 [105] | Pro-inflammatory | 167 | 1.70 (p value 0.001) | 1 SD change | Day 7 |
| Nucleated red blood cells Menk 2018 [87] | Erythrocyte progenitor cell, pro-inflammatory | 404 | 3.21 (1.93–5.35) | > 220/μL | |
| Peptidase inhibitor 3 Wang 2017 [105] | Anti-inflammatory | 167 | 0.50 (p value 0.003) | 1 SD change | Day 1 |
| Peptidase inhibitor 3 Wang 2017 [105] | Anti-inflammatory | 167 | 0.43 (p value 0.001) | 1 SD change | Day 3 |
| Peptidase inhibitor 3 Wang 2017 [105] | Anti-inflammatory | 167 | 0.70 (p value 0.18) | 1 SD change | Day 7 |
| Plasminogen activator inhibitor 1 Cartin-Ceba 2015 [67] | Coagulation | 100 | 0.96 (0.62–1.47) | Per log10 | |
| Plasminogen activator inhibitor 1 (activity) Tsangaris 2009 [101] | Coagulation | 52 | 1.30 (0.84–1.99) | Per 1 unit increase | |
| Procalcitonin Adamzik 2013 [58] | Inflammation | 47 | 1.01 (0.025–1.2) | Per log10 | |
| Procalcitonin Rahmel 2018 [94] | Inflammation | 119 | 0.999 (0.998–1.001) | |
| Protein C McClintock 2008 [86] | Coagulation | 50 | 0.5 (0.2–1.0) | Per natural log | |
| Protein C Tsangaris 2017 [102] | Coagulation | 53 | 3.58 (0.73–15.54) | < 41.5 mg/dL | |
| Receptor for advanced glycation end products Calfee 2008 [62] | Alveolar epithelial injury | 676 | 1.41 (1.12–1.78) | Per log10 | Tidal volume 12 mL/kg |
| Receptor for advanced glycation end products Calfee 2008 [62] | Alveolar epithelial injury | 676 | 1.03 (0.81–1.31) | Per log10 | Tidal volume 6 mL/kg |
| Receptor for advanced glycation end products Calfee 2015 [66] | Alveolar epithelial injury | 100 | 1.98 (1.18–3.33) | Per log10 | Single centre |
| Receptor for advanced glycation end products Calfee 2015 [66] | Alveolar epithelial injury | 853 | 1.16 (1.003–1.34) | Per log10 | Multicentre |
| Receptor for advanced glycation end products Cartin-Ceba 2015 [67] | Alveolar epithelial injury | 100 | 0.81 (0.50–1.30) | Per log10 | |
| Receptor for advanced glycation end products Mrozek 2016 [89] | Alveolar epithelial injury | 119 | 3.1 (1.1–8.9) | | |
| Soluble suppression of tumourigenicity-2 Bajwa 2013 [61] | Myocardial strain and inflammation | 826 | 1.47 (0.99–2.20) | ≥ 534 ng/mL (day 0) | Day 0 |
| Soluble suppression of tumourigenicity-2 Bajwa 2013 [61] | Myocardial strain and inflammation | 826 | 2.94 (2.00–4.33) | ≥ 296 ng/mL (day 3) | Day 3 |
| Soluble triggering receptor expressed on myeloid cells-1 Lin 2010 [80] | Pro-inflammatory | 63 | 6.338 (1.607–24.998) | Per log 10 | |
| Surfactant protein-A Eisner 2003 [72] | Alveolar epithelial injury | 565 | 0.92 (0.68–1.27) | Per 100 ng/mL increment | |
Table 4 Risk ratios for ARDS mortality in the ARDS population (continued)

| Reference | Biomarker role in ARDS | Sample size | Risk ratio (95% CI) | Cut-off | Comment |
|-----------|------------------------|-------------|---------------------|---------|---------|
| Surfactant protein D Calfee 2011 [64] | Alveolar epithelial injury | 547 | 1.55 (1.27–1.88) | Per natural log | |
| Surfactant protein D Calfee 2015 [66] | Alveolar epithelial injury | 100 | 1.33 (0.82–2.14) | Per log10 | Single centre |
| Surfactant protein D Calfee 2015 [66] | Alveolar epithelial injury | 853 | 1.09 (0.95–1.24) | Per log10 | Multicentre |
| Surfactant protein D Eisner 2003 [72] | Alveolar epithelial injury | 565 | 1.21 (1.08–1.35) | Per 100 ng/mL increment | |
| Thrombin–antithrombin III complex Cartin-Ceba 2015 [67] | Coagulation | 100 | 1.05 (0.53–2.05) | Per log10 | |
| High sensitivity troponin I Metkus 2017 [88] | Myocardial injury | 1057 | 0.94 (0.64–1.39) | 1st, 5th quintile | |
| Cardiac troponin T Rivara 2012 [96] | Myocardial injury | 177 | 1.44 (1.14–1.81) | Per 1 ng/mL increase | |
| Trombomodulin Sapru 2015 [98] | Coagulation | 449 | 2.40 (1.52–3.83) | Per log10 | Day 0 |
| Trombomodulin Sapru 2015 [98] | Coagulation | 449 | 2.80 (1.69–4.66) | Per log10 | Day 3 |
| Tumour necrosis factor alpha Lin 2010 [80] | Pro-inflammatory | 63 | 3.691 (0.668–20.998) | Per log 10 | |
| Tumour necrosis factor receptor-1 Calfee 2011 [64] | Pro-inflammatory | 547 | 1.58 (1.20–2.09) | Per natural log | |
| Tumour necrosis factor receptor-1 Parsons 2005 [91] | Pro-inflammatory | 562 | 5.76 (2.63–12.6) | Per log10 | |
| Tumour necrosis factor receptor-2 Parsons 2005 [91] | Pro-inflammatory | 376 | 2.58 (1.05–6.31) | Per log10 | |
| Uric acid Lee 2019 [77] | Antioxidant | 237 | 0.549 (0.293–1.030) | ≥ 3.00 mg/dL | |
| Von Willebrand factor Calfee 2011 [64] | Endothelial activation, coagulation | 547 | 1.57 (1.16–2.12) | Per natural log | |
| Von Willebrand factor Calfee 2012 [65] | Endothelial activation, coagulation | 931 | 1.51 (1.20–1.90) | Per log10 | |
| Von Willebrand factor Calfee 2015 [66] | Endothelial activation, coagulation | 853 | 1.83 (1.46–2.30) | Per log10 | Multicentre |
| Von Willebrand factor Cartin-Ceba 2015 [67] | Endothelial activation, coagulation | 100 | 2.93 (0.90–10.7) | Per log10 | |
| Von Willebrand factor Ware 2004 [107] | Endothelial activation, coagulation | 559 | 1.6 (1.4–2.1) | Per SD increment | |

Biomarkers in BALF

| Reference | Biomarker role in ARDS | Sample size | Risk ratio (95% CI) | Cut-off | Comment |
|-----------|------------------------|-------------|---------------------|---------|---------|
| Angiopoietin-2 Tsangaris 2017 [102] | Increased endothelial permeability | 53 | 11.18 (1.06–117.48) | > 705 pg/mL | |
| Fibrocyte percentage Quesnel 2012 [93] | Pro-fibrotic | 92 | 6.15 (2.78–13.64) | > 6% | |
| Plasminogen activator inhibitor 1 (activity) Tsangaris 2009 [101] | Coagulation | 52 | 0.37 (0.06–2.35) | Per 1 unit increase | |
| Procollagen III Clark 1995 [69] | Pro-fibrotic | 117 | 3.6 (1.2–10.7) | ≥ 1.75 U/mL | |
| Procollagen III Forel 2015 [73] | Pro-fibrotic | 51 | 5.02 (2.06–12.25) | ≥ 9 µg/L | |
| Transforming growth factor alpha Madtes 1998 [83] | Pro-fibrotic | 74 | 2.3 (0.7–7.0) | > 1.08 pg/mL | |
| Transforming growth factor beta 1 Forel 2018 [74] | Pro-fibrotic | 62 | 1003 (0.986–1.019) | |
multivariate data because of heterogeneity of the included studies, as transformation of raw data, biomarker concentration cut-offs, time until outcome, and the variables used in the multivariate analyses varied widely between studies. This could be an incentive to standardize the presentation of ARDS biomarker research in terms of statistics and outcome for future analyses or to make individual patient data accessible.

ARDS biomarkers are presumed to reflect the pathophysiology of ARDS, characterized by alveolar-capillary membrane injury, high permeability alveolar oedema, and migration of inflammatory cells [3]. Previously, Terpstra et al. [19] proposed that biomarkers for ARDS development were correlated with alveolar tissue injury, whereas biomarkers for ARDS mortality correlated more with inflammation. In this systematic review, we found that the majority of biomarkers tested for both ARDS development and mortality were surrogates for inflammation. However, following qualitative inspection, biomarkers for inflammation were not evidently associated with either ARDS development or mortality. In contrast, markers for alveolar epithelial injury (plasma RAGE and SpD) and endothelial permeability (plasma Ang-2) seem to be associated with ARDS development. Therefore, we should consider how we intend to use (a set of) biomarkers in patients with ARDS.

A biomarker for ARDS development should be specific for ARDS, i.e. a biomarker that reflects alveolar injury or alveolar-capillary injury. Half of plasma biomarkers for ARDS development included in this study reflected inflammation. An increase in inflammatory biomarkers is known to correlate with increased disease severity scores [71, 97, 110]. In turn, the majority of studies in this review found significantly higher disease severity scores in the critically ill patients that eventually developed ARDS. Thus, plasma biomarkers for inflammation rather represented an estimation of disease severity and its associated increased risk for the development of ARDS. In addition, biomarkers for inflammation in plasma lack the specificity to diagnose ARDS, as they are unlikely to differentiate sepsis with ARDS from sepsis without ARDS. In contrast, locally sampled biomarkers for inflammation, for example in the alveolar space, could potentially diagnose ARDS [111]. Biomarkers used for ARDS mortality or for the identification of less heterogeneous ARDS phenotypes do not require to be ARDS specific, provided that they adequately predict or stratify patients with ARDS.

The heterogeneity of ARDS has been recognized as a major contributor to the negative randomized controlled trial results among patients with ARDS [11]. Therefore, it is necessary to identify homogeneous ARDS phenotypes that are more likely to respond to an intervention. This is known as predictive enrichment [112]. Previously, patients with ARDS have been successfully stratified based on clinical parameters, such as ARDS risk factor (pulmonary or extra-pulmonary) or PaO2/FiO2 ratio [113]. ARDS biomarkers could be used to stratify patients with ARDS based on biological or pathophysiological phenotype. For example, trials of novel therapies designed to influence vascular permeability may benefit from preferentially enrolling patients with high Ang-2 concentrations. Recently, clinical parameters have been combined with a set of biomarkers in a retrospective latent class analysis. In three trials, two distinct phenotypes were found: hyperinflammatory and hypoinflammatory ARDS [16, 17]. Patients with the hyperinflammatory phenotype had reduced mortality rate with higher positive end-expiratory pressures and with liberal fluid treatment, whereas the trials themselves found no difference between the entire intervention groups. The next step is to validate the identification of ARDS phenotypes based on latent class analysis in prospective studies. An adequate combination of biomarkers and clinical parameters remains to be established. Until now, there is no list of biomarkers that are associated with ARDS development or mortality independently of clinical parameters. This systematic review may guide the selection of ARDS biomarkers used for predictive enrichment.

### Table 4 Risk ratios for ARDS mortality in the ARDS population (Continued)

| Biomarker role in ARDS | Sample size | Risk ratio (95% CI) | Cut-off |
|------------------------|-------------|---------------------|---------|
| Immunomodulation        | 47          | 6.5 (1.7–25)        | ≥ 7.4%  |
| Alveolar epithelial injury (elastin breakdown) | 579       | 1.36 (1.02–1.82)    | Per log10 |
| Oxidative injury        | 576         | 0.33 (0.20–0.54)    | Per log10 |
| Oxidative injury        | 576         | 0.43 (0.28–0.66)    | Per log10 |

**Abbreviations:** ALI acute lung injury, BALF bronchoalveolar lavage fluid, SD standard deviation

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This systematic review has limitations. First, the intent of this systematic review was to perform a meta-analysis. However, we decided not to perform a meta-analysis, as the biomarker data handling and outcomes varied widely among studies, and pooling would have resulted in a non-informative estimate [21]. Arguably, this is a positive result, as it refrains us from focusing on the few biomarkers that could be pooled in a meta-analysis and guides us into a direction were multiple biomarkers combined with other parameters are of interest. In a heterogeneous syndrome as ARDS, the one biomarker probably does not exist. Second, the first sampling moment varied between sampling at ICU admission until 72 h following ICU admission. Initially, ARDS is characterized by an exudative phase followed by a second proliferative phase and late fibrotic phase [3]. The moment of sampling likely influences biomarker concentrations, as both alveolar membrane injury and inflammation increase during the exudative phase. This is also seen in six biomarkers that have been measured at separate days, resulting in a significant change in adjusted OR for four biomarkers (Table 4) [61, 98, 104, 105]. Third, the aim of this systematic review was to assess the independent risk effects of biomarkers measured in various bodily fluid compartments. However, the majority of studies assessed biomarkers in plasma. It remains to be answered whether other bodily fluid compartments, for example from the airways and alveolar space themselves, might outperform ARDS biomarkers in plasma, especially for ARDS development. Fourth, all studies found in this systematic review used a clinical definition of ARDS as standard for ARDS diagnosis. Given the poor correlation between a clinical diagnosis and a histopathological diagnosis of ARDS, these studies are diagnosing a very heterogeneous disease syndrome [7–10]. In order to actually evaluate ARDS development, biomarkers should be compared to a histopathological image of DAD, although acquiring histology poses great challenges by itself. Fifth, as only biomarkers assessed in multivariate analyses were included in this study, new promising biomarkers evaluated in univariate analyses were excluded from this study. Lastly, non-significant biomarkers in multivariate analyses were more likely not to be reported, although some studies report non-significant results nonetheless.

Conclusion
In here, we present a list of biomarkers for ARDS mortality and ARDS development tested in multivariate analyses. In multiple studies that assessed Ang-2 and RAGE, high plasma levels were associated with an increased risk of ARDS development. We did not find a biomarker that independently predicted mortality in all studies that assessed the biomarker. Furthermore, biomarker data reporting and variables used in multivariate analyses differed greatly between studies. Taken together, we should look for a combination of biomarkers and clinical parameters in a structured approach in order to find more homogeneous ARDS phenotypes. This systematic review may guide the selection of ARDS biomarkers for ARDS phenotyping.
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