Early View

Review

Systematic review of diagnostic methods for Acute Respiratory Distress Syndrome

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Please cite this article as: Hagens LA, Heijnen NFL, Smit MR, et al. Systematic review of diagnostic methods for Acute Respiratory Distress Syndrome. ERJ Open Res 2020; in press (https://doi.org/10.1183/23120541.00504-2020).

This manuscript has recently been accepted for publication in the ERJ Open Research. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

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Systematic review of diagnostic methods for Acute Respiratory Distress Syndrome

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Word count: 3382

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Take home message:

Diagnostic accuracy for diagnosis of Acute Respiratory Distress Syndrome (ARDS) is associated with risk of bias. There is a lack of validated diagnostic tests in an unbiased setting, we emphasize the necessity for quality driven diagnostic research in ARDS.
ABSTRACT

Rationale:
Acute Respiratory Distress Syndrome (ARDS) is currently diagnosed by the Berlin definition, which does not include a direct measure of pulmonary oedema, endothelial permeability or pulmonary inflammation. We hypothesized that biomarkers of these processes have good diagnostic accuracy for ARDS.

Methods:
Medline and Scopus were searched for original diagnostic studies using minimal invasive testing. Primary outcome was the diagnostic accuracy per test and categorised by control group. The methodological quality was assessed with Quadas-2 tool. Biomarkers that had an area under the Receiver Operating Characteristic curve (AUROCC) of more than 0.75 and were studied with minimal bias against an unselected control group were considered to be promising.

Results:
Forty-four articles were included. The median AUROCC for all evaluated tests was 0.80 (25th to 75th percentile: 0.72 – 0.88). The type of control group influenced the diagnostic accuracy (p=0.0095). Higher risk of bias was associated with higher diagnostic accuracy (AUROCC 0.75 for low bias, 0.77 for intermediate bias and 0.84 for high bias studies; p=0.0023). Club Cell protein 16 and soluble receptor for advanced glycation end-products in plasma and two panels with biomarkers of oxidative stress in breath showed good diagnostic accuracy in low bias studies that compared ARDS patients to an unselected intensive care unit (ICU) population.
Conclusion:

This systematic review revealed only four diagnostic tests fulfilling stringent criteria for a promising biomarker in a low bias setting. For implementation into the clinical setting, prospective studies in a general unselected ICU population with good methodological quality are needed.
INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is characterized by the acute onset of non-cardiogenic pulmonary oedema and hypoxemia and is associated with a high mortality and morbidity [1], [2]. The combination of increased permeability of the endothelium and injury to the alveolar epithelium results in protein rich alveolar fluid [3]. Procoagulatory and inflammatory proteins and metabolites of oxidative stress are abundant in the alveoli of ARDS patients [1]. Translational evidence suggests that lung injury can be initiated via alveolar inflammation as well as endothelial injury [3].

ARDS is currently diagnosed by means of the Berlin definition [4], [5]. The criteria utilize information that is commonly available at the bedside: it captures hypoxemia via PaO2/FiO2 and alveolar oedema via bilateral opacities on chest radiography. Interpretation of chest images gives inconsistent results, which makes diagnosing ARDS subjective and challenging [6]. But even without this limitation, chest radiography can only diagnose alveolar oedema after onset and it will never identify the molecular mechanism resulting in alveolar oedema.

A diagnostic test that captures extra-vascular lung water earlier or that identifies the pathophysiological mechanisms resulting in lung injury is likely to lead to better diagnostic accuracy for the diagnosis of ARDS. Biomarkers are objective, can be derived minimally invasive from plasma, urine, bronchoalveolar lavage fluid or breath, and can be reflective of key biological pathways known to be involved in ARDS development [3]. A clear diagnostic biomarker could help clinical decisions in several matters: (1) earlier recognition of pulmonary oedema can help to prevent fluid overload and (2) identification of the biological pathways resulting in lung injury can inform targeted treatments in personalized medicine randomized controlled trials (RCTs). Up to now, a clear diagnostic biomarker has not been identified [7], though
the accuracy of a biomarker may be biased by the quality of the performed study and therefore it is important to evaluate potential bias when reviewing the currently available evidence.

The aim of this review is to give an overview of the minimal invasive diagnostic tests assessing the pathogenesis of ARDS to early and objectively diagnose ARDS in patients on the intensive care unit (ICU). We hypothesized that tests for (1) pulmonary oedema, (2) endothelial permeability, (3) pulmonary inflammation, (4) coagulation and (5) oxidative stress have good diagnostic accuracy, and that the diagnostic accuracy is lower in well-conducted studies than in biased studies.
METHODS

Search

A systematic review following preferred reporting items for systematic reviews was performed [8]. We searched Medline and Scopus for potentially relevant articles up to 9 June 2020. The following terms were used: ARDS, Acute Lung Injury (ALI), inflammation, biomarker, cytokine, breath, oedema, lung water, diagnosis, diagnostic, human, adult. The exact search can be found in the supplemental material (Supplemental methods). Two researchers (LB and LH) independently reviewed the abstracts and/or full text manuscripts and selected relevant articles. Disagreements were solved in a consensus meeting. The review protocol is registered at PROSPERO (www.crd.york.ac.uk/prospero, CRD42020186974).

Selection criteria

Inclusion criteria were (1) original research with a diagnostic purpose that (2) reported the diagnostic accuracy of (3) a minimal invasive test for (4) pathophysiological mechanisms of ARDS (5) comparing patients having ARDS to relevant other patients. A relevant control group was defined as patients at risk for ARDS, for example receiving mechanical ventilation or respiratory support. Studies with a focus on treatment or prediction of ARDS were excluded. Other exclusion criteria were articles not available in English, animal or preclinical studies, studies in children, and unclear reference or index test. Finally, studies were excluded if the primary endpoint, diagnostic accuracy of the index test, was not available and could not be inferred from the data. Details are given in appropriate paragraphs below.

Reference test
The first American-European consensus criteria (AECC) date back to 1994 [9]. Studies from 1994 until 2012 were included if they used the applicable AECC definition or criteria that were closely related. Patients within the category of “acute lung injury” were included in this review as having ARDS, since the in 2012 introduced Berlin definition included this group as mild ARDS. For studies from 2012 onward the Berlin definition was introduced and this ARDS definition was used as reference test [2].

**Index test**

The index tests were categorized into the following domains, regarding the pathophysiological mechanisms: (1) endothelial permeability, (2) pulmonary oedema, (3) inflammation, (4) coagulation or (5) oxidative stress. The index test should assess one of the pathophysiological mechanisms of ARDS, so studies looking into diagnostic tools based on cardiac function or, for example, terms in the electronic health record were excluded. Second, the tests were categorized based on the sample material: plasma, breath, alveolar fluid or other. The limit for invasiveness of the test was set at performing a bronchoalveolar lavage (BAL) procedure, all tests more invasive than this method were excluded. Effectively, this excludes any type of biopsy. Last, index tests were categorized on diagnostic accuracy, a potentially clinically relevant diagnostic accuracy was defined as an area under the receiver operating characteristics curve (AUROCC) of above 0.75.

**Outcome and data extraction**

The primary outcome was the AUROCC of the diagnostic test. If not available, sensitivity and specificity were used in a secondary analysis. In case both results
were not reported and the paper included a figure with individual data points, we extracted the data from the figure and recalculated the AUROCC, sensitivity and specificity. If this was unsuccessful, the study was excluded. The study population was categorized into: (1) general ICU patients, (2) cardiopulmonary surgery or cardiac ICU patients, (3) sepsis patients or (4) highly selected populations (such as only trauma patients or organ transplant patients). The control group was categorized into: (1) unselected ICU patients, (2) patients with cardiopulmonary oedema (CPE) and (3) patients with (suspected) pneumonia.

Methodological assessment and categorization
The methodological quality of each article was assessed with the QUADAS-2 tool [10]. Risk of bias was assessed concerning patient selection, blinding and use of index test, blinding and use of reference test and regarding patient flow. Timing of the test was considered to have a low risk of bias when the index test and reference test were performed on the same day or subsequent day. All tests that were performed later were classified as having a high risk of bias. For the assessment of the overall methodological quality of the papers, a cumulative score was calculated. The risk and concern scores were classified as follows: ‘High’ 1 point; ‘Unclear’ 0.5 points; ‘Low’ 0 points, resulting in a cumulative score between 0 and 6. Based on the cumulative score, studies were categorized into tertiles: “Low”, “Intermediate” and “High” biased studies with the following cut-offs: Low: ≤1.5, Intermediate: >1.5 and ≤2.5, High: >2.5 points.

Statistical analysis
The AUROCC was summarized for each index test (so one study investigating multiple tests would provide multiple AUROCCs) and stratified for the following domains:

- pathophysiological processes: endothelial permeability, pulmonary oedema, inflammation, coagulation or oxidative stress
- population: general ICU, sepsis, cardiac care unit (CCU) or a specific group
- control group: unselected ICU, CPE or pneumonia
- sample material: plasma, breath, alveolar fluid or other
- quality of the study: low, intermediate or high risk of bias

Subsequently the AUROCC was compared between the groups with one-way ANOVA. Significant results, defined as a p-value <0.05, were further studied using post-hoc analysis with pairwise T-tests. The influence of the processes resulting in changes in biomarkers concentration, like tested material, pathophysiological mechanism, population and control group on the association between bias and diagnostic accuracy, was evaluated using two-way ANOVA. For studies that reported sensitivity and specificity, meta-analysis of diagnostic accuracy was performed using the mada package to visually confirm any association that was found for AUROCC in the primary analysis [11]. All analysis were performed in R version 3.6.1 using the R-studio interface.
RESULTS

The Medline and Scopus search was last updated on 9 June 2020 and revealed 1096 articles, of which 958 remained after removing duplicates (Figure 1). Title screening resulted in 143 eligible articles, of which 52 remained after reading the abstracts. After reading the full texts, 44 articles were included (Figure 1; Table 1). Assessment of the included articles yielded a total of 84 index tests, including 68 different types of tests. Plasma biomarkers were most frequently studied (48/84; 57%). Categorization based on pathophysiological mechanisms led to the following numbers: 39 tests for inflammation, 20 for endothelial permeability, 15 for pulmonary oedema, 8 for oxidative stress and 2 for coagulation (Table S1). The following populations were included in the studies: 29 studies with general ICU population (66%), 9 studies with a specific population (20%), 5 studies with sepsis patients (11%) and 1 study with a CCU population (2%). The control group consisted of patients with CPE in 11 studies (25%) and pneumonia in 2 study (5%). The other studies included a cohort of ICU patients that did not have CPE or pneumonia specifically (70%).
| Author      | Year | Population | ARDS     | Control group | Biomarkers                                                                 |
|------------|------|------------|----------|---------------|-----------------------------------------------------------------------------|
| Abbas [12] | 2017 | ICU general | Berlin   | ICU all       | MBG/creatinine                                                              |
| Aman [13]  | 2011 | ICU general | Other    | ICU all       | Albumin, transferrin                                                        |
| Arif [14]  | 2002 | ICU general | Other    | CPE           | Transferrin, total protein, albumin, PLI                                    |
| Bai [15]   | 2017 | Specific group | Berlin | ICU all       | Glutamate increase                                                          |
| Bajwa [16] | 2013 | ICU general | AECC     | CPE           | sST2                                                                       |
| Bauer [17] | 2000 | Specific group | Other  | CPE           | TNF-alfa, IL-1 beta, IL-6                                                   |
| Bersten [18]| 2001 | ICU general | Other    | ICU all       | SP-A, SP-B                                                                 |
| Bos [19]   | 2014a| ICU general | Berlin   | ICU all       | Three metabolites identified by GCMS                                        |
| Bos [20]   | 2014b| ICU general | Berlin   | ICU all       | Pattern recognized by e-nose 1, pattern recognized by e-nose 2             |
| Brett [21] | 1998 | ICU general | AECC     | ICU all       | NO                                                                          |
| Bursten [22]| 1996 | ICU general | AECC     | ICU all       | Acyl ratio                                                                  |
| Copetti [23]| 2008 | ICU general | AECC     | CPE           | 7 characteristics of lung ultrasound                                       |
| Determann [24]| 2009| ICU general | AECC     | Pneumonia     | CC16, CC16 increase, KL-6, sRAGE, SP-D                                   |
| Reference         | Year  | Setting                  | System | Sample Size | ICU Type | Biomarkers Details                                                                 |
|-------------------|-------|--------------------------|--------|-------------|----------|------------------------------------------------------------------------------------|
| El Solh [25]      | 2005  | Specific group           | AECC   | 34          | ICU all  | 17                                                                                 |
| Fremont [26]      | 2010  | Specific group           | AECC   | 85          | ICU all  | 107 Model with 7 biomarkers, model with 3 biomarkers                              |
| Grissom [27]      | 2003  | ICU general              | AECC   | 6           | ICU all  | 33 PAF-AH                                                                          |
| Herrera [28]      | 1988  | Cardiac Care Unit        | Other  | 11          | CPE      | 23 PPK                                                                             |
| Hoeboer [29]      | 2015  | Specific group           | Berlin | 1790        | ICU all  | 143 Albumin                                                                        |
| Howrylak [30]     | 2009  | ICU general              | Berlin | 53          | ICU all  | 48 Genetic model                                                                   |
| Huang [31]        | 2019  | Sepsis                   | AECC   | 21          | ICU all  | 21 IG percentage                                                                   |
| Izquierdo-Garcia [32] | 2018  | Specific group           | AECC   | 31          | Pneumonia 25 Metabolic biomarker panel                                             |
| Jabaudon [33]     | 2018  | ICU general              | Berlin | 188         | ICU all  | 34 sRAGE0, sRAGE1, sRAGE 1-0                                                      |
| Jorens [34]       | 1992  | ICU general              | Other  | 12          | ICU all  | 15 IL-8                                                                            |
| Kietzmann [35]    | 1993  | ICU general              | Other  | 29          | ICU all  | 7 Maximum H2O2                                                                     |
| Kushimoto [36]    | 2012  | ICU general              | Other  | 59          | CPE      | 207 PVPI, ITBV                                                                      |
| LeTourneau [37]   | 2012  | ICU general              | AECC   | 10          | ICU all  | 19 EVLWi, PaO2/FiO2, EDI                                                           |
| Lin [38]          | 2012  | ICU general              | Berlin | 129         | ICU all  | 83 Copeptin                                                                         |
| Lin [39]          | 2013  | ICU general              | AECC   | 28          | CPE      | 78 HBP                                                                              |
| Lin [40]          | 2018  | ICU general              | AECC   | 34          | CPE      | 87 CC16, CRP                                                                        |
| Liu [41]          | 2015  | Specific group           | Berlin | 10          | ICU all  | 18 MDA, NO, H2O2, 8-isoprostaglandin F2 alfa,                                      |
| Author     | Year | Condition | Criteria | Study | Biomarkers                                                                 |
|------------|------|-----------|----------|-------|-----------------------------------------------------------------------------|
| Liu [42]   | 2017 | Sepsis    | AECC     | ICU all | 19 TNF-alfa, IL-8, SOD, IL-10                                               |
| Monnet [43]| 2007 | ICU general | Other   | CPE    | 36 PVPI, ELVWi/GEDVi                                                        |
| Park [44]  | 2017 | ICU general | Berlin  | ICU all | 39 SP-D                                                                     |
| Sato [45]  | 2004 | ICU general | AECC    | ICU all | 28 PARK7                                                                    |
| Sekiguchi [46]| 2015 | ICU general | AECC    | CPE    | 42 CCUS prediction model                                                    |
| Shan [47]  | 2016 | ICU general | Berlin  | ICU all | 45 suPAR, hsCRP, PCT                                                        |
| Sweeney [48]| 2018 | ICU general | Berlin  | ICU all | 148 Model with 7 genes                                                     |
| Verheij [49]| 2005 | ICU general | Other   | CPE    | 13 PLI, PTCER, Ga/Tc slope/intercept, Ga/Tc monoexponential TER            |
| Ware [50]  | 2013 | Sepsis    | AECC     | ICU all | 100 Model with 5 biomarkers                                               |
| Ware [51]  | 2017 | Specific group | Berlin  | ICU all | 78 Model with 11 biomarkers, model with 2 biomarkers                      |
| Wu [52]    | 2019 | Specific group | Berlin  | ICU all | 73 Tissue factor                                                            |
| Xue [53]   | 2015 | Sepsis    | Other   | ICU all | 94 CC16                                                                      |
| Yeh [54]   | 2017 | Sepsis    | AECC     | ICU all | 18 Gas6                                                                     |
| Zhou [55]  | 2019 | ICU general | Berlin  | ICU all | 21 Panel with 9 metabolites                                               |

Footnote: Abbreviations (in alphabetical order): AECC = American-European consensus criteria, ARDS = Acute Respiratory Distress Syndrome, CC16 = Club Cell protein 16, CCUS = critical care ultrasonography, CPE = cardiac pulmonary oedema, CRP = c-reactive protein, EDI = EVLW physiologic dead space index, EVLW = extra vascular lung water, Gas6 = growth arrest-specific...
gene 6, Ga/Tc = gallium/technetium, GCMS = gas chromatography mass spectrometry, H2O2 = hydrogen peroxide, HBP = heparin-binding protein, hsCRP = high sensitive c-reactive protein, ICU = intensive care unit, IG = immature granulocyte, IL = interleukin, ITBV = intrathoracic blood volume, KL = Krebs von den Lungen, MDA = malondialdehyde, NO = nitric oxide, PAF-AH = platelet-activating factor acetylhydrolase, PAI-1 = plasminogen activator inhibitor-1, PARK7 = Parkinson disease 7, PCT = procalcitonin, PLI = pulmonary leak index, PPK = prekallikrein, PTCER = pulmonary transcapillary escape rate, PVPI = extravascular lung water/pulmonary blood volume, SOD = superoxide dismutase, SP = surfactant protein, sRAGE = soluble receptor for advanced glycation end-products, sST2 = soluble suppression of tumorigenicity-2, suPAR = soluble urokinase-type plasminogen activator receptor, TER = transcapillary escape rate, TNF = tumor necrosis factor.
Diagnostic accuracy for diagnosing ARDS

For 74 of the 84 tests (88%) the AUROCC was available. The median AUROCC was 0.80 with an interquartile range (IQR) from 0.72 to 0.88. A good diagnostic accuracy (AUROCC >0.75) was shown in 47 of the 74 tests (64%), spread over all different processes associated with ARDS development.

Diagnostic accuracy was higher in tests comparing ARDS patients to CPE patients (median AUROCC: 0.89, IQR: [0.81-0.93]), than in ARDS patients compared to general ICU patients (median AUROCC: 0.78, IQR: [0.71-0.84], p=0.0095). The AUROCC was not different between studies with control group of pneumonia patients compared to unselected ICU patients (p=0.82) or between pneumonia patients compared to CPE patients (p=0.14; Figure 2). No differences in AUROCC were found for the type of studied pathophysiological mechanism (p=0.76), the studied biological material (p=0.51) and the population (p=0.60).

Sensitivity and specificity were available or could be calculated for 46/84 (55%) studies. Similar patterns regarding the influence of the type of test, the studied biological material, the population and the control group were found when these studies were evaluated based on a single cut-off (Figure S1-S4).

Assessment of bias in study methodology

The methodological quality as assessed by the QUADAS-2 tool is shown in Table 2. The final score varied among studies, with a cumulative score with median of 2.0, IQR: [1.5 to 3.00]. Categorization into tertiles based on the cumulative score led to 14 studies in the “Low” bias category, 17 studies in the category “Intermediate” and 13 studies were in the “High” category (Table 2). The risk of bias was most frequently
observed for patient selection, blinding of the index test and in the timing of the index test.
| Author    | Year | Domain 1 Risk score | Domain 2 Risk score | Domain 3 Risk score | Domain 4 Risk score | Cumulative score | Risk of bias category |
|-----------|------|---------------------|---------------------|---------------------|---------------------|------------------|----------------------|
| Abbas     | 2017 | 1                   | 0                   | 0.5                 | 0.5                 | 2.5              | Intermediate         |
| Aman      | 2011 | 1                   | 0                   | 0.5                 | 0                   | 2                | Intermediate         |
| Arif      | 2002 | 1                   | 1                   | 0.5                 | 0                   | 3.5              | High                |
| Bai       | 2017 | 1                   | 1                   | 0.5                 | 0                   | 3                | High                |
| Bajwa     | 2013 | 1                   | 1                   | 1                   | 0                   | 3.5              | High                |
| Bauer     | 2000 | 0                   | 0                   | 0.5                 | 0.5                 | 1                | Low                 |
| Bersten   | 2001 | 0.5                 | 1                   | 0.5                 | 0                   | 2                | Intermediate         |
| Bos       | 2014a| 0                   | 0                   | 0                   | 0                   | 0.5              | 0.5                 | Low                 |
| Bos       | 2014b| 0                   | 0                   | 0                   | 0                   | 0.5              | 0.5                 | Low                 |
| Brett     | 1998 | 1                   | 0                   | 0.5                 | 0                   | 0.5              | 2                   | Intermediate         |
| Bursten   | 1996 | 0.5                 | 0                   | 0.5                 | 0                   | 0.5              | 1.5                 | Low                 |
| Copetti   | 2008 | 0                   | 1                   | 1                   | 0                   | 2                | Intermediate         |
| Determann | 2009 | 1                   | 1                   | 1                   | 0                   | 3.5              | High                |
| El Solh   | 2005 | 0                   | 1                   | 1                   | 0.5                 | 2                | 2.5                 | Intermediate         |
| Fremont   | 2010 | 1                   | 0                   | 0.5                 | 0.5                 | 1                | 3                   | High                |
| Grissom   | 2003 | 0.5                 | 0                   | 1                   | 0.5                 | 1                | 3                   | High                |
| Herrera   | 1988 | 0.5                 | 0                   | 0.5                 | 0                   | 0.5              | 2                   | Intermediate         |
| Author                  | Year | Country | Code | Risk | Control | Quality | Design | Methodology | Impact | Findings |
|-------------------------|------|---------|------|------|---------|---------|--------|-------------|--------|----------|
| Hoeboer [29]            | 2015 | 0       | 0    | 0    | 0       | 0       | 0      | 0           | 0      | Low      |
| Howrylak [30]           | 2009 | 1       | 0    | 0.5  | 0       | 0       | 1      | 2.5         | Intermediate |
| Huang [31]              | 2019 | 0       | 1    | 0.5  | 0.5     | 0       | 0      | 2           | Intermediate |
| Izquierdo-Garcia [32]    | 2018 | 1       | 1    | 0.5  | 0.5     | 0       | 0      | 3           | High |
| Jabadon [33]            | 2018 | 0.5     | 0    | 0    | 0       | 0       | 0      | 0.5         | Low |
| Jorens [34]             | 1992 | 1       | 0    | 1    | 0.5     | 0       | 0      | 2.5         | Intermediate |
| Kietzmann [35]          | 1993 | 0.5     | 0    | 1    | 0.5     | 0       | 1      | 3           | High |
| Kusimoto [36]           | 2012 | 1       | 0    | 0    | 0       | 0       | 0      | 1           | Low |
| LeTourneau [37]         | 2012 | 0.5     | 0    | 0.5  | 0       | 0       | 1      | 2           | Intermediate |
| Lin [38]                | 2012 | 0       | 0    | 0.5  | 0       | 0       | 0      | 0.5         | Low |
| Lin [39]                | 2013 | 0       | 0    | 0.5  | 0.5     | 0       | 0      | 1           | Low |
| Lin [40]                | 2018 | 0       | 0    | 0.5  | 0       | 0       | 0.5    | 1           | Low |
| Liu [41]                | 2015 | 1       | 1    | 0.5  | 0.5     | 0       | 0.5    | 3.5         | High |
| Liu [42]                | 2017 | 0       | 1    | 0.5  | 0       | 0.5     | 0      | 2           | Intermediate |
| Monnet [43]             | 2007 | 1       | 0    | 1    | 0.5     | 0       | 0      | 2.5         | Intermediate |
| Park [44]               | 2017 | 1       | 0    | 1    | 0.5     | 0       | 1      | 3.5         | High |
| Sato [45]               | 2004 | 1       | 1    | 1    | 0.5     | 0       | 1      | 4.5         | High |
| Sekiguchi [46]          | 2015 | 1       | 0    | 0    | 0       | 0       | 0      | 1           | Low |
| Shan [47]               | 2016 | 1       | 0    | 1    | 0       | 0       | 0.5    | 2.5         | Intermediate |
| Sweeney [48]            | 2018 | 1       | 0    | 0    | 1       | 1       | 1      | 4           | High |
| Author       | Year | Value | Value | Value | Value | Value | Value | Value | Type   |
|--------------|------|-------|-------|-------|-------|-------|-------|-------|--------|
| Verheij [49] | 2005 | 1     | 0     | 1     | 0     | 0     | 1     | 3     | High   |
| Ware [50]    | 2013 | 1     | 0     | 0.5   | 0     | 0     | 0     | 1.5   | Low    |
| Ware [51]    | 2017 | 1     | 0     | 0.5   | 0     | 0     | 1     | 2.5   | Intermediate |
| Wu [52]      | 2019 | 0     | 1     | 0     | 0.5   | 0     | 0.5   | 2     | Intermediate |
| Xue [53]     | 2015 | 1     | 0     | 1     | 0.5   | 0     | 0     | 2.5   | Intermediate |
| Yeh [54]     | 2017 | 0     | 0     | 1     | 0     | 0     | 0     | 1     | Low    |
| Zhou [55]    | 2019 | 0.5   | 0     | 0.5   | 0     | 0     | 0.5   | 1.5   | Low    |
Association between bias and diagnostic accuracy

The risk of bias of the study was associated with the diagnostic accuracy of the index test \( p=0.0023 \). The median AUROCC was 0.75 IQR: [0.69 to 0.82] for low bias studies and 0.77 IQR: [0.72 to 0.88] for intermediate bias and 0.84 IQR: [0.79 to 0.90] for high bias studies (Figure 3). Based on the pairwise comparison, the AUROCC was significantly higher for studies in the high bias category, compared to the intermediate and low bias category \( p=0.020 \) and \( p=0.0077 \), respectively). Two-way ANOVA showed that this association was consistent after correction for the type of test \( p=0.0027 \), sample material \( p=0.0026 \), population \( p=0.0026 \) and control group \( p=0.0011 \). Figure 3 shows the diagnostic accuracy per test after stratification for risk of bias. The other comparisons are visualized in figures S5-S7 of the online supplement. The same trend was visible in the analysis of sensitivity and specificity with respect to the risk of bias (Figure S1-S4).

Low bias studies with good diagnostic accuracy

Nine tests showed a good diagnostic accuracy in the low bias group. Of these, 5 compared ARDS versus CPE and 4 compared ARDS versus the general ICU population. The studies comparing ARDS versus ICU patients measured biomarkers in plasma and metabolites in exhaled breath. The plasma biomarkers assessed were Club Cell protein 16 (CC16) and soluble receptor for advanced glycation end-products (sRAGE), assessing inflammation and permeability. In exhaled breath a panel with 3 metabolites and a panel with 9 metabolites were assessed. The three metabolites describe oxidative stress, the 9 metabolites most likely too, but no clear reporting on this topic was available. The first three studies performed the test on the
day of ARDS diagnosis or the day after, providing early information on diagnosis of ARDS. For the last test it was unclear at what time it was performed.
DISCUSSION

When comparing patients with ARDS to patients who are also admitted to the ICU, only four studies yielded a good diagnostic accuracy with a limited risk of potential bias. We identified CC16 and sRAGE in plasma and two exhaled breath tests for biomarkers of oxidative stress as tests that currently have the strongest rationale for further validation. This review provides strong evidence that the diagnostic accuracy of minimally invasive tests for the diagnosis of ARDS is highly dependent on the potential bias of the study and the type of control group that is included.

Diagnostic accuracy varied widely between tests and studies included in this review. We identified that the inclusion of CPE patients as a control group consistently resulted in a higher diagnostic accuracy, suggesting that CPE can be better distinguished from ARDS than ICU patients at risk for ARDS or pneumonia patients. An attractive explanation could be that the test differentiates between protein rich and hydrostatic oedema, but this explanation was rejected because most tests did not evaluate this phenomenon directly and could still separate these groups. For example, cardiac injury markers are also able to distinguish between CPE and ARDS, but instead of being a relevant test for ARDS it rather signifies the homogeneity of the CPE population [56]. Importantly, ARDS patients differ from CPE patients in many more aspects than the type of pulmonary oedema alone. For example, ARDS patients showed increased levels of inflammation parameters compared to CPE patients, but this is not necessarily related to ARDS but may be due to an underlying syndrome such as sepsis, pneumonia or pancreatitis. Indeed, when compared to an unselected ICU population with similar risk factors as the ARDS patients, these markers had a lower diagnostic accuracy.
The risk of bias assessed by the QUADAS-2 tool was strongly associated with the diagnostic accuracy of the study. A large part of the studies showed risk of bias due to the method of patient selection, performance and interpretation and timing of the index test. Unfortunately this relationship and the fact that biased studies are known to overestimate diagnostic accuracy [57], makes it hard to rely on results from studies with a considerable amount of bias. It will be necessary to redo studies with tests showing good diagnostic accuracy but then in a low bias setting before any firm conclusions can be drawn.

Focussing on studies with good diagnostic accuracy with low risk of bias, 9 tests remained. Only 4 of them compared ARDS to an unselected ICU population. One test assessed the plasma concentration of CC16 [40]. This protein is suggested to protect the lungs against oxidative stress as well as inflammation [58]. However, CC16 also is a marker of increased permeability of the epithelial barrier, and therefore seems to be involved in multiple processes of ARDS development [40], [58]. Another test assessed sRAGE in plasma, which is released by lung inflammation and leads to epithelial injury, and is therefore a marker of increased permeability [33], [59]. The other two were exhaled breath tests [19], [55], with the major advantage that it can be obtained non-invasively. One test assessed a panel of three biomarkers, octane, acetaldehyde and 2/3-methylheptane, that reflect oxidative stress [19]. Of these three compounds, octane explained most of the diagnostic accuracy. Octane is generated through oxygenation of oleic acid and previous data suggest that ARDS is associated with an increased concentration of oleic acid in the circulation [60]. The other breath test assessed a larger biomarker panel, with 9
exhaled breath biomarkers, not clearly reflective of one pathophysiological mechanism [55]. A drawback of the exhaled breath test is the fact that these are experimental and are therefore not directly suitable for clinical implementation. All tests seem to relate to oxidative stress, inflammation and increased permeability in the lungs which are all known to be important in the early course of ARDS, and are related to pulmonary pathophysiology directly.

This is the first review to systematically assess the diagnostic accuracy of minimally invasive techniques for ARDS while considering potential biases of each study. Our analyses show that it is pivotal to evaluate the methodological quality of the study to reveal the confounding factors while interpreting the results. This approach is one of the most important strengths of this study. Furthermore, papers not reporting diagnostic accuracy directly, were not excluded when we could deduce the accuracy from figures showing individual data points. To our knowledge, no other study in critical care has utilized this approach up to now. Finally, we did not limit the definition of ARDS to those patients with a PaO2/FiO2 below 200mmHg by including patients who were labelled as “acute lung injury” according to the 1994 AECC definition. Since ARDS nowadays involves a heterogeneous population, of which patients with mild ARDS are a large part, it is important to recognize also this group [61]. Another strength is the exclusion of studies that used healthy volunteers as control group leaving only more relevant control groups and hopefully resulting in a more accurate comparison between similarly ill patients.

The main limitation of this review is the small number of studies that is left in each category after stratification. This sometimes led to groups with few studies, for
example only one study assessed the CCU patients and only two studies compared
diagnosis of ARDS with patients with a pneumonia. With regard to pneumonia, it is
questionable if unilateral pneumonia is the appropriate control group for ARDS as
many patients with ARDS have pneumonia and because unilateral and bilateral
pneumonia in the ICU have similar outcomes [62]. Furthermore, both studies that
compared ARDS to pneumonia scored high on the risk of bias. A second limitation is
the fact that the AUROCC was not for all studies reported. Therefore, the analysis
was performed in two parts with two different approaches, which yielded similar
results. We also acknowledge that the diagnostic tests cannot be categorized into
completely distinct groups, for example, there is considerable overlap between
markers of oxidative stress and inflammation and our attempted separation of the two
is arbitrary. Another limitation of this study is the fact that the definition of ARDS has
changed over the years and therefore the “case-definition” is slightly different
between studies, which might have confounded the diagnostic accuracy of specific
tests. Finally, it should be noted however that we assessed multiple diagnostic tests
described in a single paper as independent tests, which they potentially are not. To
our knowledge, there is no adequate multi-level alternative to study this phenomenon
otherwise.

Results of this review show that there is no validated minimal invasive method to
diagnose ARDS in an unselected ICU population. Four promising tests were
identified in a low bias setting and these warrant validation. New diagnostic studies
should better attempt to minimise bias and should be reported according to STARD
guidelines [63].
A diagnostic test does not have to separate ARDS patients perfectly. This is likely impossible due to the biological heterogeneity observed in ARDS patients. Indeed, another way to evaluate these results is to appreciate the heterogeneity that is shown and advocate a personalized approach based on pathophysiological characteristics of each patient shown through the diagnostic tests that are described here [64]. A biomarker may have value when it identifies a phenotype that consistently responds to a specific type of treatment, a so-called treatable trait [65].
CONCLUSION

There is no minimally invasive diagnostic test for ARDS that is validated in a low bias setting against an adequate control group. Many studies that evaluated diagnostic tests for ARDS showed risk of bias, which makes it hard to rely on the reported diagnostic accuracy. The plasma concentration of CC16, sRAGE and two panels of oxidative stress biomarkers in exhaled breath did show high diagnostic accuracy in low bias setting and warrant external validation. For implementation into the clinical setting, prospective studies in a general unselected ICU population with good methodological quality are needed.

ACKNOWLEDGEMENTS

Lieuwe Bos is supported by Health Holland via the Dutch Lung Foundation (longfonds) industry-academia partnership and via the Dirkje Postma Award. They had no role in the design, conduction or interpretation of this review.
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Flowchart of article selection.
AUROCC = area under the receiver operating characteristics curve. Each dot represents a diagnostic test, multiple tests could be evaluated per study. Red: high risk of bias, blue: intermediate risk of bias, green: low risk of bias. AUROCC was higher in tests comparing ARDS patients to CPE patients, then in ARDS patients compared to general ICU patients \((p=0.0095)\). The AUROCC was not different between studies with control group of pneumonia patients compared to unselected ICU patients \((p=0.82)\) or between pneumonia patients compared to CPE patients \((p=0.14)\).
AUROCC = area under the receiver operating characteristics curve. Each dot represents a diagnostic test, multiple tests could be evaluated per study. Red: high risk of bias, blue: intermediate risk of bias, green: low risk of bias. The AUROCC was significantly higher in the group with high risk of bias, compared to the intermediate and low bias group (p=0.020 and p=0.00077 respectively).
ONLINE SUPPLEMENT

Systematic review of diagnostic methods for Acute Respiratory Distress Syndrome

Authors:
Laura A. Hagens [1], Nanon F.L. Heijnen [3], Marry R. Smit [1], Marcus J. Schultz [1,4,5], Dennis C.J.J. Bergmans [3], Ronny M. Schnabel [3], Lieuwe D.J. Bos [1,2]
On behalf of the DARTS consortium.

Content:
- Supplemental methods
- Checklist of reported items
- Online tables (S1)
- Online figures (S1-S7)
- References
SUPPLEMENTAL METHODS

Search:

Exact search Medline:

(ARDS[title] OR "Acute respiratory distress syndrome"[title] OR ALI[title] OR "acute lung injury"[title]) AND (diagnosis OR diagnostic) AND (biomarker OR breath OR cytokine OR inflammation OR edema OR "lung water") AND (Humans[Mesh] AND adult[MeSH]) NOT review

Exact search Scopus:

( TITLE ( ards ) OR TITLE ( "acute respiratory distress syndrome" ) OR TITLE ( ali ) OR TITLE ( "acute lung injury" ) AND TITLE-ABS-KEY ( ( inflammation OR biomarker OR cytokine OR breath ) OR ( edema OR "lung water" ) ) AND TITLE-ABS-KEY ( diagnosis OR diagnostic ) ) AND ( EXCLUDE ( DOCTYPE, "re" ) ) AND ( LIMIT-TO ( EXACTKEYWORD, "Human" ) OR LIMIT-TO ( EXACTKEYWORD, "Humans" ) OR LIMIT-TO ( EXACTKEYWORD, "Adult" ) )
**CHECKLIST OF REPORTED ITEMS**

**Prisma checklist**

| Section/topic       | #  | Checklist item                                                                 | Reported on page # |
|--------------------|----|-------------------------------------------------------------------------------|--------------------|
| **TITLE**          |    |                                                                              |                    |
| Title              | 1  | Identify the report as a systematic review, meta-analysis, or both.           | 1                  |
| **ABSTRACT**       |    |                                                                              |                    |
| Structured summary | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3-4                |
| **INTRODUCTION**   |    |                                                                              |                    |
| Rationale          | 3  | Describe the rationale for the review in the context of what is already known. | 5-6                |
| Objectives         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6                  |
| **METHODS**        |    |                                                                              |                    |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 7                  |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7                  |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 7                  |
| Search             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | S2                 |
| Study selection    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7-9                |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7-9                |
| Data items         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7-10               |
| Section                              | Item | Description                                                                                                                                                                                                                                                                                                                                 | Page |
|--------------------------------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Risk of bias in individual studies  | 12   | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                                                                                       | 9    |
| Summary measures                     | 13   | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                                                                                  | 8-9  |
| Synthesis of results                 | 14   | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.                                                                                                                                                                                              | 8-9  |
| Risk of bias across studies          | 15   | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                                                                                                                                                      | N/A  |
| Additional analyses                  | 16   | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                                                                                                                                                   | 10   |
| RESULTS                              |      |                                                                                                                                                                                                                                                                                                                                              |      |
| Study selection                      | 17   | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                                                                                                                                                    | 11   |
| Study characteristics                | 18   | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                                                                                                                                                       | 12-15, S5-S11, S16-18 |
| Risk of bias within studies          | 19   | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                                                                                                                                                    | 16-22 |
| Results of individual studies        | 20   | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.                                                                                                                                                     | N/A  |
| Synthesis of results                 | 21   | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                                                                                                                                                         | N/A  |
| Risk of bias across studies          | 22   | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                                                                                                                                             | N/A  |
| Additional analysis                  | 23   | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                                                                                                                                                          | S12-S15 |
| DISCUSSION                           |      |                                                                                                                                                                                                                                                                                                                                              |      |
| Summary of evidence                  | 24   | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                                                                                                                                                                        | 23-25|
| Limitations                          | 25   | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                                                                                                                                                         | 25-26|
| Conclusions                          | 26   | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                                                                                                                                                       | 28   |
| FUNDING                              |      |                                                                                                                                                                                                                                                                                                                                              |      |
| Funding                              | 27   | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                                                                                                                                                       | 28   |

N/A = not applicable.
## ONLINE TABLES

### Table S1:
Overview of all index tests.

| Author  | Test                  | Timing                                      | Material | What is tested? | ROC | Sensitivity | Specificity | Cut-off | Unit   | Bias    |
|---------|-----------------------|---------------------------------------------|----------|-----------------|-----|-------------|------------|---------|--------|---------|
| Abbas (1) | MBG/creatinine       | Unclear.                                    | Other    | Pulmonary water | 0.88| 84          | 93         | 95      | pg/mg  | Intermediate |
| Aman (2)  | Albumin              | Within 12 hours after meeting sepsis criteria or 3 hours after major surgery. | Plasma   | Permeability    | 0.8 | 79          | 64         | 17.05   | g/L    | Intermediate |
| Aman (2)  | Transferrin          |                                             | Plasma   | Permeability    | 0.78| 93          | 65         | 1.05    | g/L    | Intermediate |
| Arif (3)   | Transferrin          | Within 72 hours after admission.            | Plasma   | Permeability    | 0.98| 87          | 100        | 1.5     | g/L    | High    |
| Arif (3)   | Total protein        |                                             | Plasma   | Permeability    | 0.9 | 81          | 87         | 56      | g/L    |         |
| Arif (3)   | Albumin              |                                             | Plasma   | Permeability    | 0.77| 44          | 100        | 24      | g/L    |         |
| Arif (3)   | PLI                  |                                             | Plasma   | Pulmonary water | 0.98| 87          | 100        | 16.3    | *10^-3/min  |
| Bai (4)    | Glutamate increase   | At admission.                               | Plasma   | Inflammation    | 0.79| N.D.        | N.D.       | 99.89   | µM     | High    |
| Bajwa (5)  | sST2                 | Unclear.                                    | Plasma   | Inflammation    | 0.98| 91          | 94         | 142     | ng/mL  | High    |
| Bauer (6)  | TNF-alfa             | Within 24 hours after diagnosis.            | Plasma   | Inflammation    | 0.71| 50          | 90         | 51.87   | pg/mL  | Low     |
| Bauer (6)  | IL-1 beta            |                                             | Plasma   | Inflammation    | 0.88| 87          | 75         | N.D.    | N.D.   |         |
| Bauer (6)  | IL-6                 |                                             | Plasma   | Inflammation    | 0.61| 96          | 35         | 14.81   | pg/mL  |         |
| Bersten (7)| SP-A                 | Within 24 hours after inclusion.            | Plasma   | Permeability    | 0.61| N.D.        | N.D.       | N.D.    | N.D.   | Intermediate |
| Bersten (7)| SP-B                 |                                             | Plasma   | Permeability    | 0.77| 85          | 78         | 4994    | ng/mL  |         |
| Author (Ref) | Method/Parameter | Time/Condition | Sample Type | Parameter | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Notes |
|-------------|------------------|----------------|-------------|-----------|---------|---------|---------|---------|---------|--------|
| Bos (8)     | Three metabolites identified by GCMS | Unclear. | Breath | Oxidative stress | 0.78 | N.D. | N.D. | N/A | N/A | Low |
| Bos (9)     | Pattern recognized by e-nose 1 | Unclear. | Breath | Oxidative stress | 0.71 | N.D. | N.D. | N/A | N/A | Low |
| Bos (9)     | Pattern recognized by e-nose 2 | Unclear. | Breath | Oxidative stress | 0.73 | N.D. | N.D. | N/A | N/A | Low |
| Brett (10)  | NO | After diagnosing ARDS or after intubation | Breath | Inflammation | 0.93 | 92 | 89 | 0.149 | ppb | Intermediate |
| Bursten (11)| acyl ratio | Within 24 hours. | Plasma | Inflammation | N.D. | 84 | 87 | 1.45 | increase | Low |
| Copetti (12)| Alveolar interstitial syndrome | Unclear which time point used for test. Time points: at first day of admission and after diagnosis. | Other | Pulmonary water | N.D. | 100 | 0 | N/A | N/A | Intermediate |
| Copetti (12)| Pleural line abnormalities | | | | N.D. | 100 | 45 | N/A | N/A | |
| Copetti (12)| Lung sliding | | | | N.D. | 100 | 100 | N/A | N/A | |
| Copetti (12)| Spared areas | | | | N.D. | 100 | 100 | N/A | N/A | |
| Copetti (12)| Consolidations | | | | N.D. | 83.3 | 100 | N/A | N/A | |
| Copetti (12)| Pleural effusion | | | | N.D. | 66.6 | 5 | N/A | N/A | |
| Copetti (12)| Lung pulse | | | | N.D. | 50 | 100 | N/A | N/A | |
| Determann (13)| CC16 | On day of diagnosis. | Plasma | Inflammation | 0.91 | 80 | 92 | 18 | ng/mL | High |
| Determann (13)| CC16 increase | | | | N.D. | 90 | 92 | 0.3 | increase | |
| Study                          | Biomarkers                                                      | Timepoints                                      | Sample Type | Inflammation | Coagulation | Permeability | Other Measures               |
|-------------------------------|----------------------------------------------------------------|------------------------------------------------|-------------|--------------|-------------|--------------|------------------------------|
| KL-6                          | sRAGE                                                           |                                                |             |              |             |              |                              |
| SP-D                          |                                                               |                                                |             |              |             |              |                              |
| El Solh (14)                  | PAI-1                                                           | Within 8 hours after intubation               | Alveolar fluid | 0.71         | N.D.        | N.D.         | N.D.                        |
|                               | PAI-1                                                           |                                                | Plasma      | 0.63         | N.D.        | N.D.         | N.D.                        |
|                               | Model with 7 biomarkers (RAGE, PCPIII, BNP, ANG2, IL-10, TNF-alfa, IL-8) |                  | Plasma      | 0.8          | N.D.        | N.D.         | N.D.                        |
| Fremont (15)                  | Model with 3 biomarkers                                        | Within 72 hours after admission.              | Plasma      | 0.93         | 82.4        | 97.1         | 1518 ng/mL                  |
|                               | Model with 3 biomarkers                                        |                                                | Plasma      | 0.65         | N.D.        | N.D.         | N.D.                        |
| Grissom (16)                  | PAF-AH                                                          | Within 96 after diagnosis.                    | Alveolar fluid | 0.83         | 63          | 100          | 37.87 mU/mL                 |
| Herrera (17)                  | PPK                                                             | Within 24 hours after diagnosis.              | Plasma      |              |             |              |                              |
| Hoeboer (18)                  | Albumin                                                         | Within 24 hours after fever onset.            | Plasma      | 0.62         | 71          | 58           | 20 g/L                      |
| Howrylak (19)                 | Genetic model                                                  | Within 48 hours after admission.              | Plasma      | 0.89         | 100         | 50           | N/A                         |
| Huang (20)                    | IG percentage                                                  | At admission.                                 | Plasma      | 0.821        | N.D.        | N.D.         | N.D.                        |
| Izquierdo-Garcia (21)          | Metabolic biomarker panel                                      | Within 24 hours after admission.              | Plasma      | N.D.         | 100         | 91           | N/A                         |
| Jabaudon (22)                 | sRage0                                                          | At admission.                                 | Plasma      | 0.71         | N.D.        | N.D.         | N.D.                        |
| Study            | Indicator | Time Point                                | Measurement | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Category |
|------------------|-----------|-------------------------------------------|-------------|---------|---------|---------|---------|---------|----------|
| Jorens (23)      | IL-8      | Within 12 hours after diagnosis.          | Inflammation| 0.63    | 0.73    | 0.67    | 299.3   | pg/mL   | Intermediate |
| Kietzmann (24)   | maximum H2O2 | Within the first 7 days.              | Inflammation| 0.7     | 0.71    | 0.84    | 468.6   | nmol/L  | High       |
| Kushimoto (25)   | PVPI      | On day of enrollment, within 5 days after onset of acute respiratory failure. | Permeability| 0.886   | N.D.    | N.D.    | N.D.    | N.D.    | Low       |
|                  | ITBV      |                                           | Pulmonary water| 0.471   | N.D.    | N.D.    | N.D.    | N.D.    | Low       |
| LeTourneau (26)  | EVLWi     | Within 48 hours after meeting ARDS criteria. | Pulmonary water| 0.75    | 63      | 88      | 10      | ml/kg PBW | Intermediate |
|                  | PaO2/FiO2 |                                           |             | 0.71    | N.D.    | N.D.    | N.D.    | N.D.    | Low       |
|                  |            |                                           |             | 0.77    | N.D.    | N.D.    | N.D.    | N.D.    | Low       |
| Lin (27)         | Copeptin  | Within 12 hours after admission.          | Inflammation| 0.823   | 60.9    | 88.2    | 40.11   | pmol/L  | Low       |
| Lin (28)         | HBP       | After diagnosis.                          | Permeability| 0.815   | 75      | 78.2    | 11.55   | ng/mL   | Low       |
| Lin (29)         | CC16      | Within 12 hours after admission.          | Inflammation| 0.911   | 90.4    | 79.8    | 33.3    | ng/mL   | Low       |
|                  | CRP       |                                           |             | 0.648   | 54.4    | 73.2    | N.D.    | N.D.    | Low       |
| Liu (30)         | MDA       | Two hours after graft reperfusion.        | Oxidative stress| 0.88    | N.D.    | N.D.    | N.D.    | N.D.    | High      |
|                  | NO        |                                           | Oxidative stress| 0.88    | N.D.    | N.D.    | N.D.    | N.D.    | High      |
|                  | H2O2      |                                           | Oxidative stress| 0.78    | N.D.    | N.D.    | N.D.    | N.D.    | High      |
|     |                                |                              |                               |     |     |     |     |     |
|-----|--------------------------------|------------------------------|--------------------------------|-----|-----|-----|-----|-----|
|     | 8-isoprostaglandin F2 alfa     |                              |                               |     |     |     |     |     |
|     | TNF-alfa                       |                              |                               |     |     |     |     |     |
|     | IL-8                           |                              |                               |     |     |     |     |     |
|     | SOD                             |                              |                               |     |     |     |     |     |
|     | IL-10                           |                              |                               |     |     |     |     |     |
| Liu (31) | PARK7                           | At admission.                | Plasma                         | Oxidative stress | 0.73 | 78   | 70   | 200  | ng/mL  | Intermediate |
|     | Monnet (32) | PVPI                           | At diagnosis of oedema.       | Other                         | Permeability    | 0.92 | 85   | 100  | 3    | N/A     | Intermediate |
|     | Monnet (32) | EVLW/GEDVi                     |                                |                              | Pulmonary water | 0.92 | 85   | 100  | 1.8*10^2 | N/A     |                |
| Park (33) | SP-D                            | Within 72 hours after admission. | Plasma                      | Inflammation    | 0.71 | 74   | 63   | 12.7 | ng/mL   | High          |
| Sato (34) | KL-6                            | Up to a week after diagnosis. | Plasma                        | Inflammation    | 0.9  | 75   | 100  | 393.75 | U/mL   | High          |
| Sekiguchi (35) | CCUS prediction model         | Within 4 hours after inclusion. | Other                        | Pulmonary water | 0.79 | N.D. | N.D. | ≤3    | N/A     | Low           |
| Shan (36) | suPAR                           | After diagnosis.             | Plasma                        | Inflammation    | 0.63 | N.D. | N.D. | N.D. | pg/mL   | Intermediate |
|     | hsCRP                           |                              |                               |     |     |     |     |     |
|     | PCT                             |                              |                               |     |     |     |     |     |
| Sweeney (37) | Model with seven genes        | Within 48 hours after diagnosis. | Plasma                      | Inflammation    | 0.74 | 63   | 74   | N/A  | N/A     | High          |
| Verheij (38) | PLI                             | Within 72 hours after admission. | Other                        | Permeability    | 0.94 | N.D. | N.D. | N.D. | N.D.   | High          |
|     | PTCER                           |                              |                               |     |     |     |     |     |
| Study (Ref) | Biomarker Model | Time of Measurement | Sample Type | Inflammation | Permeability | Additional Details |
|------------|-----------------|---------------------|--------------|--------------|--------------|--------------------|
| Ware (39)  | Model with 5 biomarkers (SP-D, RAGE, IL-8, CC16, IL-6) | On day 2. | Plasma | Inflammation | 0.75 | 70 | 68 | N/A | N/A | Low |
| Ware (40)  | Model with 11 biomarkers | Within 72 hours after admission. | Plasma | Inflammation | 0.78 | N.D. | N.D. | N/A | N/A | Intermediate |
|            | Model with 2 biomarkers (ang-2 and RaGE) | Within 72 hours after admission. | Plasma | Inflammation | 0.74 | N.D. | N.D. | N/A | N/A | Intermediate |
| Wu (41)    | CC16            | Within 24 hours.    | Plasma | Inflammation | 0.8 | 91 | 60 | 16.8 ng/mL | Intermediate |
| Xue (42)   | Tissue factor   | At inclusion.        | Plasma | Permeability | 0.75 | 61.7 | 80.8 | 1005.8 pg/mL | Intermediate |
| Yeh (43)   | Gas6            | Within 24 hours after admission. | Plasma | Inflammation | 0.74 | 78 | 72 | 18 ng/mL | Low |
| Zhou (44)  | Panel with 9 metabolites | Unclear. | Breath | Inflammation | 0.82 | N.D. | N.D. | N/A | N/A | Low |

N/A = not applicable. N.D. = not described.

Abbreviations (in alphabetical order): AECC = American-European consensus criteria, ARDS = Acute Respiratory Distress Syndrome, CC16 = Club Cell protein 16, CCUS = critical care ultrasonography, CPE = cardiac pulmonary oedema, CRP = c-reactive protein, EDI = EVLW physiologic dead space index, EVLW = extra vascular lung water, Gas6 = growth arrest-specific gene 6, Ga/Tc = gallium/technetium, GCMS=gas chromatography mass spectrometry, H2O2 = hydrogen peroxide, HBP =
heparin-binding protein, hsCRP = high sensitive c-reactive protein, ICU = intensive care unit, IG = immature granulocyte, IL = interleukin, ITBV = intrathoracic blood volume, KL = Krebs von den Lungen, MDA = malondialdehyde, NO = nitric oxide, PAF-AH = platelet-activating factor acetylhydrolase, PAI-1 = plasminogen activator inhibitor-1, PARK7 = Parkinson disease 7 , PCT = procalcitonin, PLI = pulmonary leak index, PPK = prekallikrein, PTCER = pulmonary transcapillary escape rate, PVPI = extravascular lung water/pulmonary blood volume, SOD = superoxide dismutase, SP = surfactant protein, sRAGE = soluble receptor for advanced glycation end-products, sST2 = soluble suppression of tumorigenicity-2, suPAR = soluble urokinase-type plasminogen activator receptor, TER = transcapillary escape rate, TNF = tumor necrosis factor.
**Figure S1:** Sensitivity and specificity, stratified per control group

Triangle: CPE (n=20)
Circle: ICU all (n=24)
Diamond: Pneumonia (n=3)

Green: low bias. Blue: intermediate bias. Red: high bias.
Figure S2: Sensitivity and specificity, stratified per population

Triangle: Sepsis (n=6)
Circle: ICU general (n=34)
Square: Specific group (n=6)
Diamond: CCU (n=1)

Green: low bias. Blue: intermediate bias. Red: high bias.
**Figure S3:** Sensitivity and specificity, stratified per material

- **Triangle:** Breath (n=2)
- **Circle:** Plasma (n=31)
- **Square:** Other (n=11)
- **Diamond:** Alveolar fluid (n=3)

*Green:* low bias. *Blue:* intermediate bias. *Red:* high bias.
**Figure S4:** Sensitivity and specificity, stratified per mechanism

Triangle: Inflammation (n=23)

Circle: Permeability (n=10)

Filled square (solid line): Pulmonary oedema (n=11)

Diamond: Coagulation (n=1)

Open square (dot-dash line): Oxidative stress (n=1)

Green: low bias. Blue: intermediate bias. Red: high bias.
Figure S5: Association between risk of bias and diagnostic accuracy, stratified per type of process measured by the test.

Caption: AUROCC = area under the receiver operating characteristics curve. No difference in AUROCC was found for the type of studied pathophysiological mechanism (p=0.76).
Figure S6: Association between risk of bias and diagnostic accuracy, stratified per tested biomaterial.

Caption: AUROCC = area under the receiver operating characteristics curve. No difference in AUROCC was found for the used material (p=0.51).
Figure S7: Association between risk of bias and diagnostic accuracy, stratified per included population.

Caption: AUROCC = area under the receiver operating characteristics curve. No difference in AUROCC was found for the different populations (p=0.60).
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