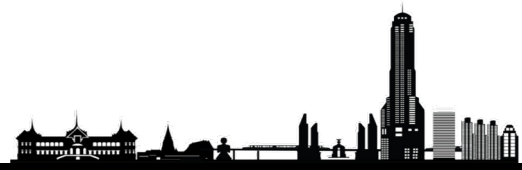
XXX International Symposium of Mechanical Ventilation of Albert Einstein Hospital
Albert Einstein Hospital, São Paolo, Brazil
August 18, 2023; 12:00–12:30 am BRT

# New Definitions of ARDS

## what changes in clinical practice?

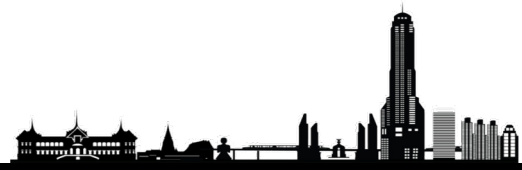


# Disclosures

- until January 2021 Xenios/Fresenius, Germany
- until January 2023 Hamilton Medical AG, Switzerland

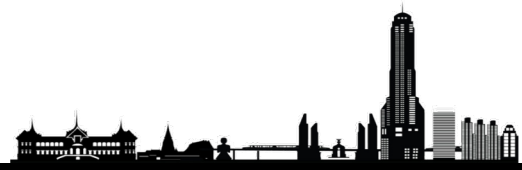


# Agenda

- two new definitions
- what does it answer
- what changes in clinical practice
- what we (still) need to know
- conclusions



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- two new definitions
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- what changes in clinical practice
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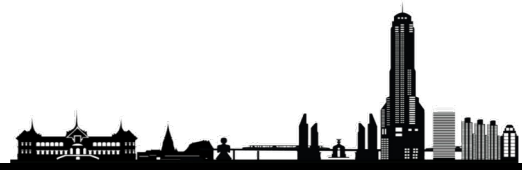

| | Murray, 1988[2] | AECC, 1994[3] | Ferguson, 2005[4] | Berlin, 2012[5] |
|---|---|---|---|---|
| Onset | Acute or chronic, not specified | Acute, not specified | Within 72 h | New or worsening within 1 week |
| Risk factor | Required | Not required | Required | Not required |
| Oxygenation (mm Hg) | $PaO_2/FiO_2$ >300 (0)<br>$PaO_2/FiO_2$ 225–299 (1)<br>$PaO_2/FiO_2$ 175–224 (2)<br>$PaO_2/FiO_2$ 100–174 (3)<br>$PaO_2/FiO_2$ <100 (4) | Acute lung injury: $PaO_2/FiO_2$ <300<br>Acute respiratory distress syndrome: $PaO_2/FiO_2$ ≤200 | $PaO_2/FiO_2$ <200 | Mild: $PaO_2/FiO_2$ 200–300<br>Moderate: $PaO_2/FiO_2$ 100–199<br>Severe: $PaO_2/FiO_2$ <100 |
| PEEP (cm $H_20$) | ≤5 (0)<br>6–8 (1)<br>9–11 (2)<br>12–14 (3)<br>≥15 (4) | Not specified | ≥10 | Minimum PEEP of 5 required |
| Infiltrates on chest radiograph | No quadrants (0)<br>One quadrant (1)<br>Two quadrants (2)<br>Three quadrants (3)<br>Four quadrants (4) | Bilateral infiltrates on a frontal chest radiograph | Bilateral airspace disease involving two or more quadrants on a frontal chest radiograph | Bilateral infiltrates involving two or more quadrants on a frontal chest radiograph or CT |
| Heart failure | .. | Pulmonary artery wedge pressure ≤17 mm Hg<br>Absence of left atrial hypertension | No clinical evidence of congestive heart failure (based on pulmonary artery catheter with or without echocardiogram) | Left ventricular failure insufficient to solely account for clinical state |
| Static compliance (mL/cm $H_20$) | ≥80 (0)<br>60–79 (1)<br>40–59 (2)<br>20–39 (3)<br>≤19 (4) | .. | Static compliance <50 (with patient sedated, tidal volume 8 mL/kg ideal bodyweight, PEEP ≥10) | Removed |
| Severity | Mild<br>Moderate<br>Severe | Based on oxygenation criteria | .. | Based on oxygenation criteria |
| Specificity for diffuse alveolar damage | Autopsy: 74%[6] (lung injury score ≥2·5) | Autopsy: 30%,[6] 50%,[7] 66%,[8] 70%[9]<br>Biopsy: 29%,[10] 47%,[11] 40%[12] | Autopsy: 69%[6] | Autospy: 45%[13]<br>Biopsy: 58%[14] |

Data in parentheses in the Murray column are scores; the total number of points scored is divided by the number of categories included, giving the Murray lung injury score. A score of 0 signifies no lung injury is present, a score of 0·1–2·5 signifies mild to moderate lung injury, and a score greater than 2·5 signifies severe lung injury. AECC=American European Consensus Conference. $PaO_2$=partial pressure of arterial oxygen. $FiO_2$=fraction of inspired oxygen. PEEP=positive end-expiratory pressure.

***Table*: Definitions of acute respiratory distress syndrome**

| | Murray, 1988[2] | AECC, 1994[3] | Ferguson, 2005[4] | Berlin, 2012[5] | Kigali modification, 2016[6] | New Global Definition of ARDS, 2023[7] |
|---|---|---|---|---|---|---|
| Onset | Acute or chronic, not specified | Acute, not specified | Within 72 h | New or worsening within 1 week | | |
| Risk factor | Required | Not required | Required | Not required | | |
| Oxygenation (mm Hg) | $PaO_2/FiO_2$ >300 (0)<br>$PaO_2/FiO_2$ 225–299 (1)<br>$PaO_2/FiO_2$ 175–224 (2)<br>$PaO_2/FiO_2$ 100–174 (3)<br>$PaO_2/FiO_2$ <100 (4) | Acute lung injury: $PaO_2/FiO_2$ <300<br>Acute respiratory distress syndrome: $PaO_2/FiO_2$ ≤200 | $PaO_2/FiO_2$ <200 | Mild: $PaO_2/FiO_2$ 200–300<br>Moderate: $PaO_2/FiO_2$ 100–199<br>Severe: $PaO_2/FiO_2$ <100 | | |
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| Oxygenation (mm Hg) | $PaO_2/FiO_2$ >300 (0)<br>$PaO_2/FiO_2$ 225–299 (1)<br>$PaO_2/FiO_2$ 175–224 (2)<br>$PaO_2/FiO_2$ 100–174 (3)<br>$PaO_2/FiO_2$ <100 (4) | Acute lung injury: $PaO_2/FiO_2$ <300<br>Acute respiratory distress syndrome: $PaO_2/FiO_2$ ≤200 | $PaO_2/FiO_2$ <200 | Mild: $PaO_2/FiO_2$ 200–300<br>Moderate: $PaO_2/FiO_2$ 100–199<br>Severe: $PaO_2/FiO_2$ <100 | $SpO_2FiO_2$ < 315 | |
| PEEP (cm $H_20$) | ≤5 (0)<br>6–8 (1)<br>9–11 (2)<br>12–14 (3)<br>≥15 (4) | Not specified | ≥10 | Minimum PEEP of 5 required | No PEEP requirement | |
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The Kigali modification was not tested for specificity for diffuse alveolar damage.

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|---|---|---|---|---|---|---|
| Onset | Acute or chronic, not specified | Acute, not specified | Within 72 h | New or worsening within 1 week | New or worsening within 1 week | New or worsening within 1 week, or new or worsening respiratory symptoms |
| Risk factor | Required | Not required | Required | Not required | Not required | ... |
| Oxygenation (mm Hg) | $PaO_2/FiO_2$ >300 (0)<br>$PaO_2/FiO_2$ 225–299 (1)<br>$PaO_2/FiO_2$ 175–224 (2)<br>$PaO_2/FiO_2$ 100–174 (3)<br>$PaO_2/FiO_2$ <100 (4) | Acute lung injury: $PaO_2/FiO_2$ <300<br>Acute respiratory distress syndrome: $PaO_2/FiO_2$ ≤200 | $PaO_2/FiO_2$ <200 | Mild: $PaO_2/FiO_2$ 200–300<br>Moderate: $PaO_2/FiO_2$ 100–199<br>Severe: $PaO_2/FiO_2$ <100 | $SpO_2FiO_2$ < 315 | Mild: $PaO_2/FiO_2$ 200–300 or $SpO_2/FiO_2$ 235–315<br>Moderate: $PaO_2/FiO_2$ 100–200 or $SpO_2/FiO_2$ 148–235<br>Severe: $PaO_2/FiO_2$ < 100 or $SpO_2/FiO_2$ < 148 |
| PEEP (cm $H_20$) | ≤5 (0)<br>6–8 (1)<br>9–11 (2)<br>12–14 (3)<br>≥15 (4) | Not specified | ≥10 | Minimum PEEP of 5 required | No PEEP requirement | Minimum of 5 PEEP required in patients receiving ventilation; flow equal or higher than 30 L/min required in patients receiving HFNO |
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| Heart failure | .. | Pulmonary artery wedge pressure ≤17 mm Hg<br>Absence of left atrial hypertension | No clinical evidence of congestive heart failure (based on pulmonary artery catheter with or without echocardiogram) | Left ventricular failure insufficient to solely account for clinical state | Left ventricular failure insufficient to solely account for clinical state | Not exclusively or primarily explained by left ventricular failure or fluid overload; not primarily attributable to atelectasis. |
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The Kigali modification was not tested for specificity for diffuse alveolar damage.

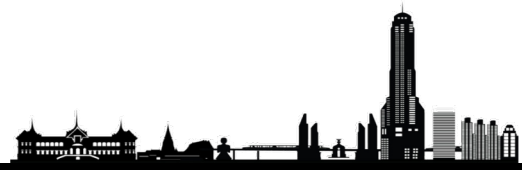
Neither PEEP or a minimum flow rate of oxygen are required for diagnosis in resource variable settings.

***Table*: Definitions of acute respiratory distress syndrome**

# Agenda

- two new definitions
- what does it answer
- what changes in clinical practice
- what we (still) need to know
- conclusions



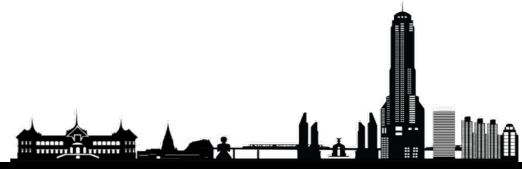



# Rethinking ARDS – if a 'Better' Definition Is the Answer, What Is the Question?

- reliability
- feasibility
- validity

Ranieri, Rubenfeld, Slutsky *Am J Resp Crit Care Med* 2023; **207**:255



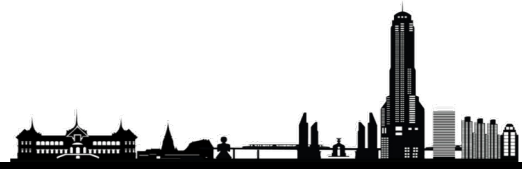



# Reliability – Are We Looking at the Same?

- $PaO_2/FiO_2$
  - PEEP, $V_T$
- CXR and LUS

Ranieri, Rubenfeld, Slutsky *Am J Resp Crit Care Med* 2023; **207**:255



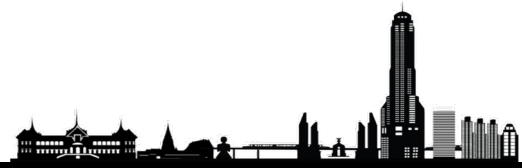



# Feasibility – Availability, Complexity, Time and Costs

- $SpO_2$ vs $PaO_2$ for $SpO_2/FiO_2$ vs $PaO_2/FiO_2$
- CXR vs LUS
- plasma biomarkers

Ranieri, Rubenfeld, Slutsky *Am J Resp Crit Care Med* 2023; **207**:255



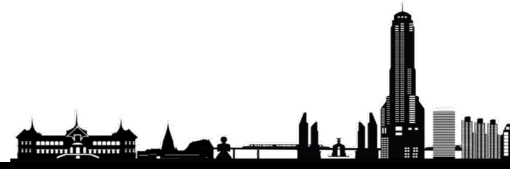
# Validity – a Test is Valid if it Measures what it Says it Measures

- face and predictive validity
- content validity
- criterion validity
- construct validity

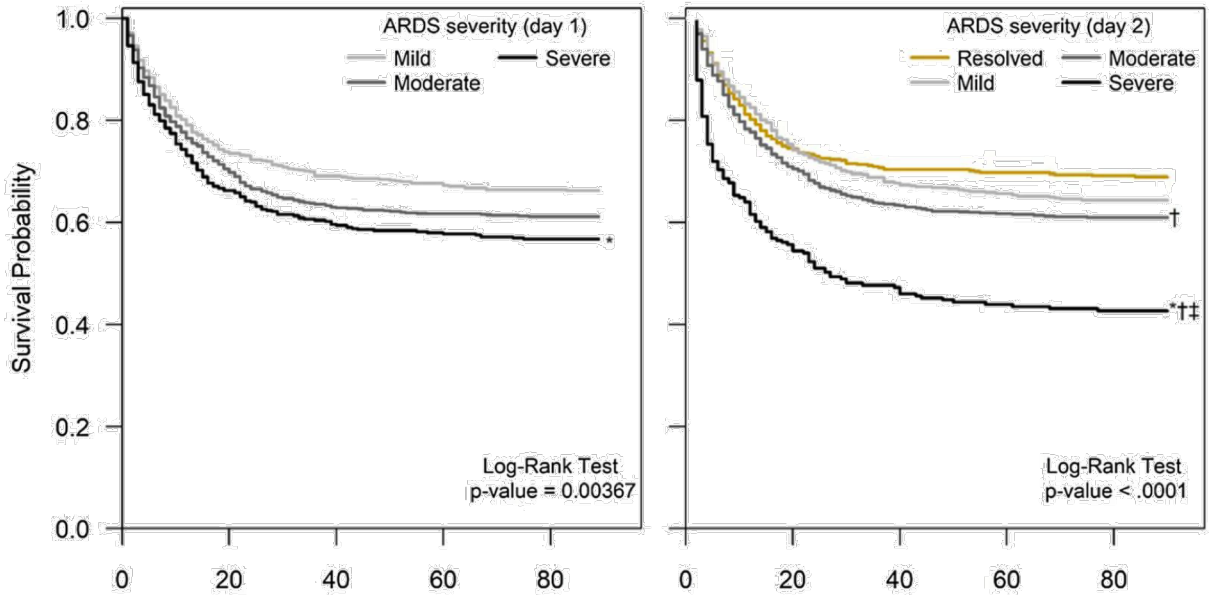
- sensibility
- accuracy
- suitability
- consistency

Ranieri, Rubenfeld, Slutsky *Am J Resp Crit Care Med* 2023; **207**:255



# Reclassification after 24 Hours Improves Prognostication





LUNG SAFE–investigators *Intensive Care Med* 2018; **44**:564

JAMA Network™

**QUESTION** For patients in the ICU who are ventilated for reasons other than ARDS, is low tidal volume superior to intermediate tidal volume?

**CONCLUSION** Among ICU patients receiving invasive ventilation, a strategy with a low tidal volume was not superior to using intermediate tidal volume.

## POPULATION

**621** Men **340** Women

ICU patients without ARDS expected to be intubated for more than 24 hours

Median age: **68** years (IQR, 59-76)

## LOCATIONS

**6**
ICUs in the Netherlands

## INTERVENTIONS

**961** Patients randomized

**477** Randomized
**475** Analyzed

### Low tidal volume

Started at tidal volume of 6 mL/kg; tidal volume then decreased in steps of 1 mL/kg predicted body weight

**484** Randomized
**480** Analyzed

### Intermediate tidal volume

Started at tidal volume of 10 mL/kg; if plateau pressure exceeded 25 cm $H_2O$, tidal volume was decreased in steps of 1 mL/kg predicted body weight

## PRIMARY OUTCOME

Number of ventilator-free days and alive at day 28

## FINDINGS


Writing Group for the PReVENT Investigators. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: a randomized clinical trial [published online October 24, 2018]. *JAMA*. doi:10.1001/jama.2018.14280

JAMA Network™

**QUESTION** In ICU patients who received invasive ventilation for reasons other than acute respiratory distress syndrome (ARDS), is a strategy with lower positive end-expiratory pressure (PEEP) noninferior to higher PEEP with respect to ventilator-free days at day 28?

**CONCLUSION** This clinical trial found that among ICU patients receiving invasive ventilation, a strategy with lower PEEP was noninferior to a strategy using higher PEEP for the outcome of ventilator-free days, supporting the use of lower PEEP in patients without ARDS.

## POPULATION

**623** Men **346** Women

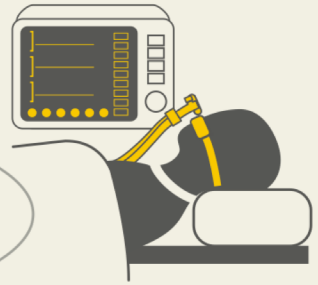
Adults without ARDS expected not to be extubated within 24 hours of intubation

Median age: **66** years

## LOCATIONS

**8** ICUs
in the Netherlands

## INTERVENTION



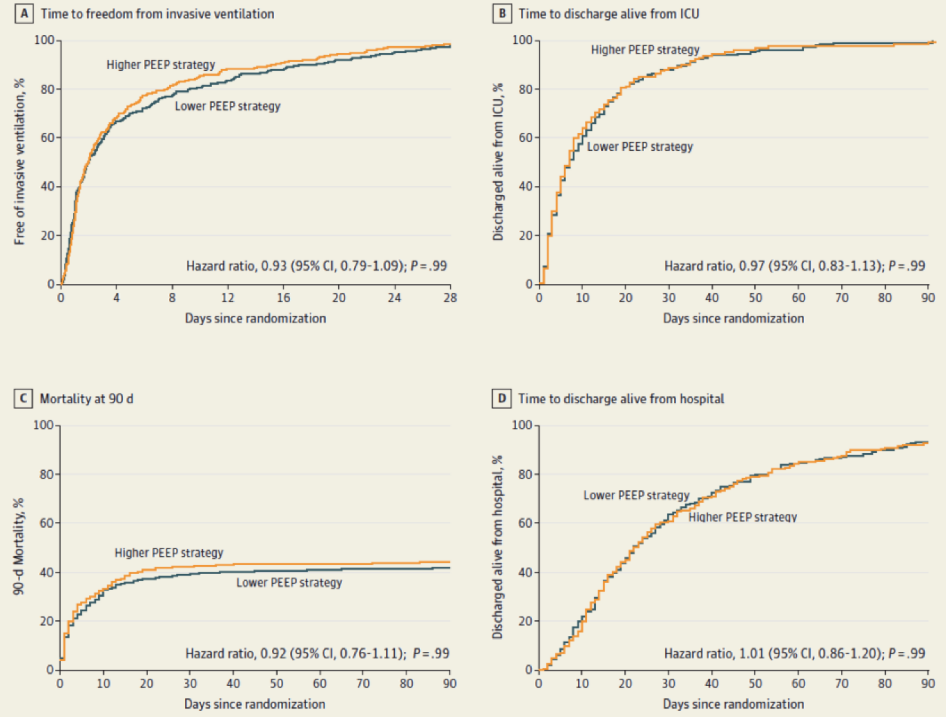
**980** Patients randomized
**969** Patients analyzed

**476**
**Lower PEEP strategy**
Lowest level between 0-5 cm $H_2O$

**493**
**Higher PEEP strategy**
Lowest level of 8 cm $H_2O$

## PRIMARY OUTCOME

Number of ventilator-free days by study day 28 (noninferiority margin of −10%)




Writing Committee for the RELAx Collaborative Group. Effect of a lower vs higher positive end-expiratory pressure strategy on ventilator-free days in ICU patients without ARDS: a randomized clinical trial. *JAMA*. Published online December 9, 2020. doi:10.1001/jama.2020.23517

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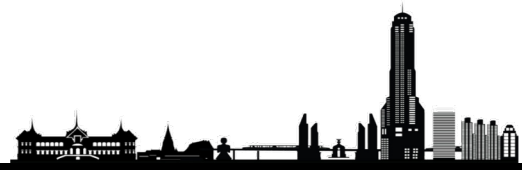
- two new definitions
- what does it answer
- what changes in clinical practice
- what we (still) need to know
- conclusions



# What Changes?

- HFNO patients can meet the definition of ARDS
- an arterial blood draw may no longer be needed, and LUS may replace CXR in some patients
- highly uncertain what it means for resource–limited settings

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- two new definitions
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- what changes in clinical practice
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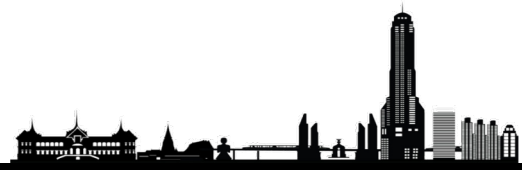

| Research Question | Answers, patient groups |
| --- | --- |
| Conduct large multicenter studies (similar to LUNG-SAFE) to determine how often patients treated with HFNO or NIV advance to requiring intubation and mechanical ventilation, including outcomes such as mortality for patients in each of these categories | |
| Assess the prognostic value and clinical implications of unilateral vs. bilateral opacities on the chest radiograph | |
| Identify the limitations to operationalization of new ARDS definition, e.g. how often pulse oximetry was not accurate for quantifying hypoxemia because of shock or skin pigmentation | |
| Carry out research, e.g. in resource limited areas, determine the incidence of ARDS diagnosis in the absence of any oxygen therapy (room air) compared to subjects treated with supplemental oxygen and the associated outcomes, specifically mortality | |
| Evaluate prognostic and clinical utility, e.g. do the oxygenation severity categories have prognostic value in non-intubated patients | |
| Evaluate the specificity of lung ultrasound diagnosis of ARDS among different operators in diverse clinical settings using different acquisition/interpretation protocols | |
| Determine the relationship of biological categories of ARDS, such as hyper- and hypoinflammatory sub-phenotypes, in the New Global Definition of ARDS and assess these biological categories in the context of sepsis and pneumonia | |
| Prospectively evaluate this New Global Definition of ARDS based on large clinical trials and observational studies around the world, including evaluation of how the new definition affects estimates of ARDS incidence | |
| Evaluate the long-term outcomes of patients diagnosed with ARDS using the New Global Definition of ARDS in prospective epidemiological studies | |

***Table:*** Areas for future prospective research

| Research Question | Answers, patient groups |
| --- | --- |
| Conduct large multicenter studies (similar to LUNG-SAFE) to determine how often patients treated with HFNO or NIV advance to requiring intubation and mechanical ventilation, including outcomes such as mortality for patients in each of these categories | |
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| Evaluate prognostic and clinical utility, e.g. do the oxygenation severity categories have prognostic value in non-intubated patients | Predictive value in COVID–19 patients receiving HFNO: worse |
| Evaluate the specificity of lung ultrasound diagnosis of ARDS among different operators in diverse clinical settings using different acquisition/interpretation protocols | |
| Determine the relationship of biological categories of ARDS, such as hyper- and hypoinflammatory sub-phenotypes, in the New Global Definition of ARDS and assess these biological categories in the context of sepsis and pneumonia | |
| Prospectively evaluate this New Global Definition of ARDS based on large clinical trials and observational studies around the world, including evaluation of how the new definition affects estimates of ARDS incidence | |
| Evaluate the long-term outcomes of patients diagnosed with ARDS using the New Global Definition of ARDS in prospective epidemiological studies | |

***Table:*** Areas for future prospective research

**QUESTION** Does a broadened Berlin definition of ARDS, in which ARDS can be diagnosed in patients who are not receiving ventilation, results in similar groups of patients receiving HFNO as in patients receiving ventilation?

**CONCLUSION** Using a broadened definition of ARDS may facilitate an earlier diagnosis of ARDS in patients receiving HFNO; however, ARDS patients receiving HFNO and ARDS patients receiving ventilation have distinct baseline characteristics and mortality rates.

## POPULATION

**344** Women **384** Men

COVID–19 patients with ARDS, including patients receiving HFNO (flow > 30 L/min)

Mean Age: **66** years

## LOCATION

**16** ICUs
in The Netherlands

## GROUPS

**728** patients with ARDS according to new definition

**229** patients
**HFNO**

**499** patients
**IMV**

## OUTCOMES

ICU mortality (primary), hospital; 28 and 90–day mortality; need for ventilation within 7 days HFNO in patients

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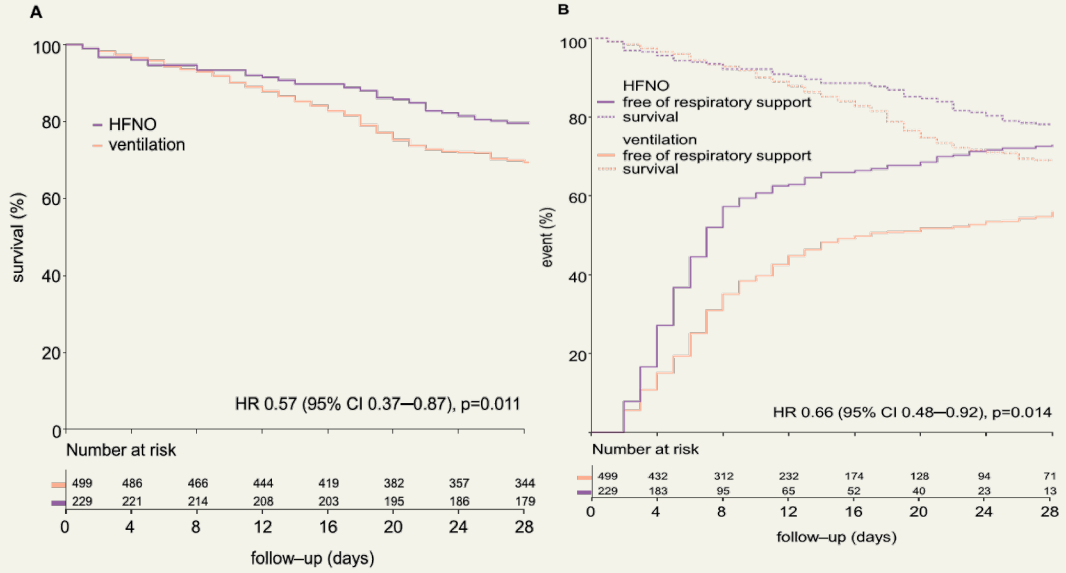


105 out of 229 (45.8%) HFNO patients needed IMV < 7 days

PRoAcT–COVID study investigators. Broadening the Berlin definition of ARDS to patients receiving high-flow nasal oxygen: an observational study in patients with acute hypoxemic respiratory failure due to COVID–19. [*AoIC* 2023; **13**:64; doi:10.1186/s13613-023-01161-6]

**QUESTION** Does a broadened Berlin definition of ARDS, in which ARDS can be diagnosed in patients who are not receiving ventilation, results in similar groups of patients receiving HFNO as in patients receiving ventilation?

**CONCLUSION** Using a broadened definition of ARDS may facilitate an earlier diagnosis of ARDS in patients receiving HFNO; however, ARDS patients receiving HFNO and ARDS patients receiving ventilation have distinct baseline characteristics and mortality rates.

## POPULATION

**344** Women **384** Men

COVID–19 patients with ARDS, including patients receiving HFNO (flow > 30 L/min)

Mean Age: **66** years

## LOCATION

**16** ICUs
in The Netherlands

## GROUPS

**728** patients with ARDS according to new definition

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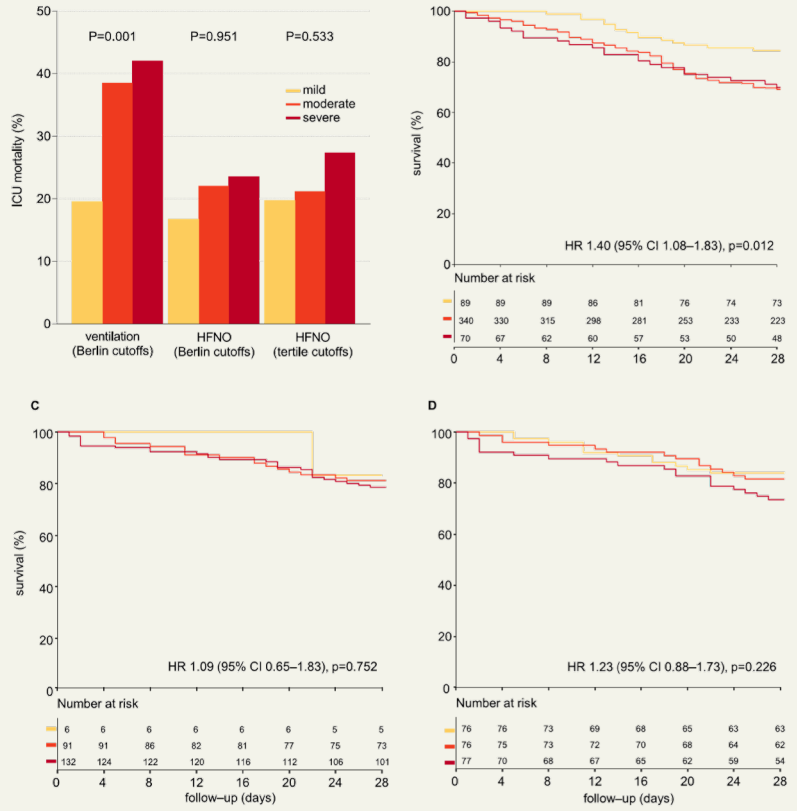
**HFNO**

**499** patients
**IMV**

## OUTCOMES

ICU mortality (primary), hospital; 28 and 90–day mortality; need for ventilation within 7 days HFNO in patients

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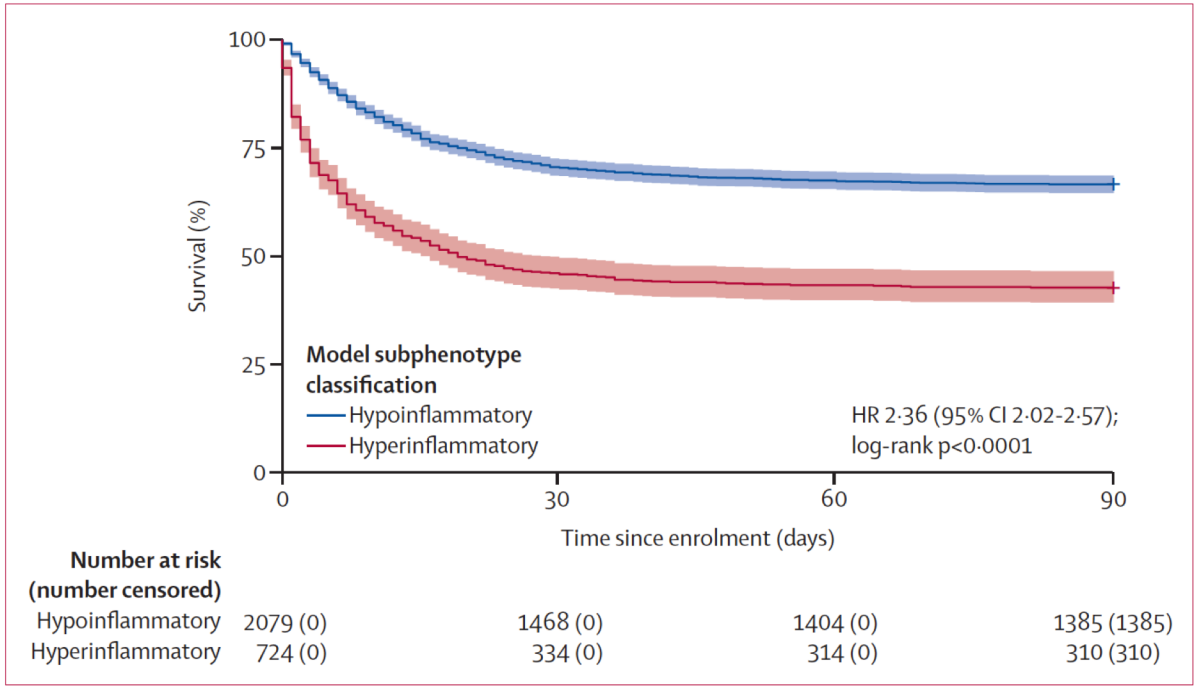
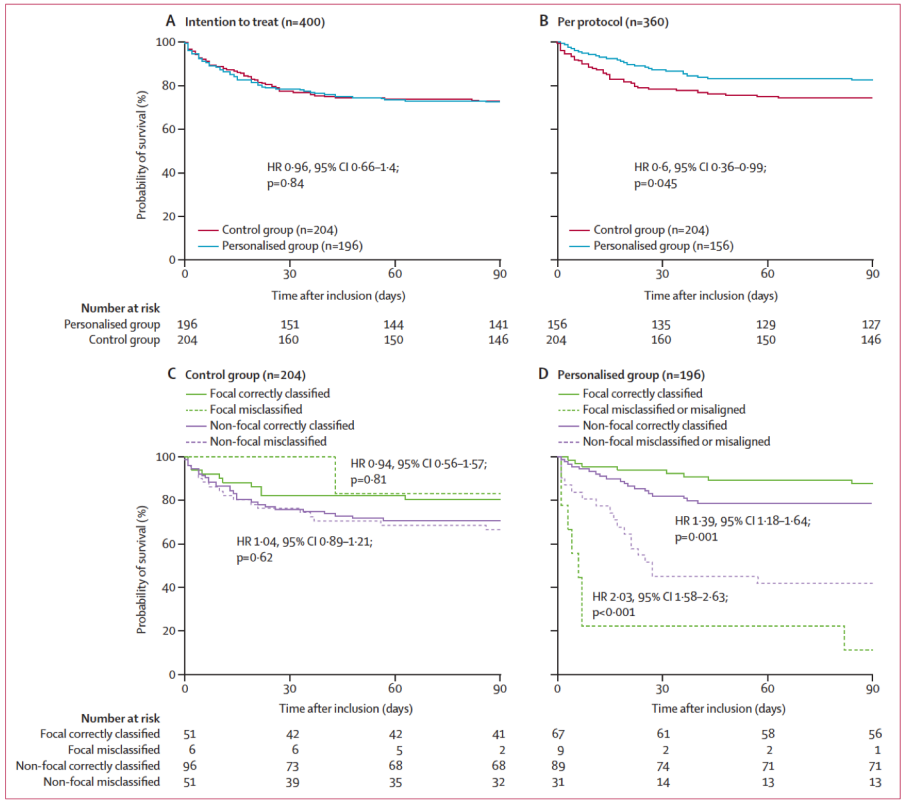
## PROGNOSTICATION

van Meenen for the PRoAcT–COVID study investigators. *Posthoc analysis of* Broadening the Berlin definition of ARDS to patients receiving high-flow nasal oxygen: an observational study in patients with acute hypoxemic respiratory failure due to COVID–19. [*in progress*]

| Research Question | Answers, patient groups |
| --- | --- |
| Conduct large multicenter studies (similar to LUNG-SAFE) to determine how often patients treated with HFNO or NIV advance to requiring intubation and mechanical ventilation, including outcomes such as mortality for patients in each of these categories | |
| Assess the prognostic value and clinical implications of unilateral vs. bilateral opacities on the chest radiograph | |
| Identify the limitations to operationalization of new ARDS definition, e.g. how often pulse oximetry was not accurate for quantifying hypoxemia because of shock or skin pigmentation | |
| Carry out research, e.g. in resource limited areas, determine the incidence of ARDS diagnosis in the absence of any oxygen therapy (room air) compared to subjects treated with supplemental oxygen and the associated outcomes, specifically mortality | |
| Evaluate prognostic and clinical utility, e.g. do the oxygenation severity categories have prognostic value in non-intubated patients | |
| Evaluate the specificity of lung ultrasound diagnosis of ARDS among different operators in diverse clinical settings using different acquisition/interpretation protocols | |
| Determine the relationship of biological categories of ARDS, such as hyper- and hypoinflammatory sub-phenotypes, in the New Global Definition of ARDS and assess these biological categories in the context of sepsis and pneumonia | |
| Prospectively evaluate this New Global Definition of ARDS based on large clinical trials and observational studies around the world, including evaluation of how the new definition affects estimates of ARDS incidence | |
| Evaluate the long-term outcomes of patients diagnosed with ARDS using the New Global Definition of ARDS in prospective epidemiological studies | |

# Subphenotypes




LUNG SAFE–investigators *Lancet RM* 2022; **10**:367

LIVE–investigators *Lancet RM* 2019; **7**:870

BJA

**QUESTION** Is there heterogeneity in treatment effects in patients enrolled in the ART, using a machine learning approach?

**CONCLUSION** Recruitment maneuvers and titrated PEEP may be harmful in ARDS patients with pneumonia or requiring vasopressor support. Driving pressure appears to modulate the association between the ART study intervention, etiology of ARDS, and mortality.

## POPULATION

**379** Women **631** Men

consecutive patients with moderate to severe ARDS

Mean Age: **51** years

## LOCATION

**120** ICUs
from **9** countries

## VENTILATION STRATEGIES

**1010** patients with moderate or severe ARDS

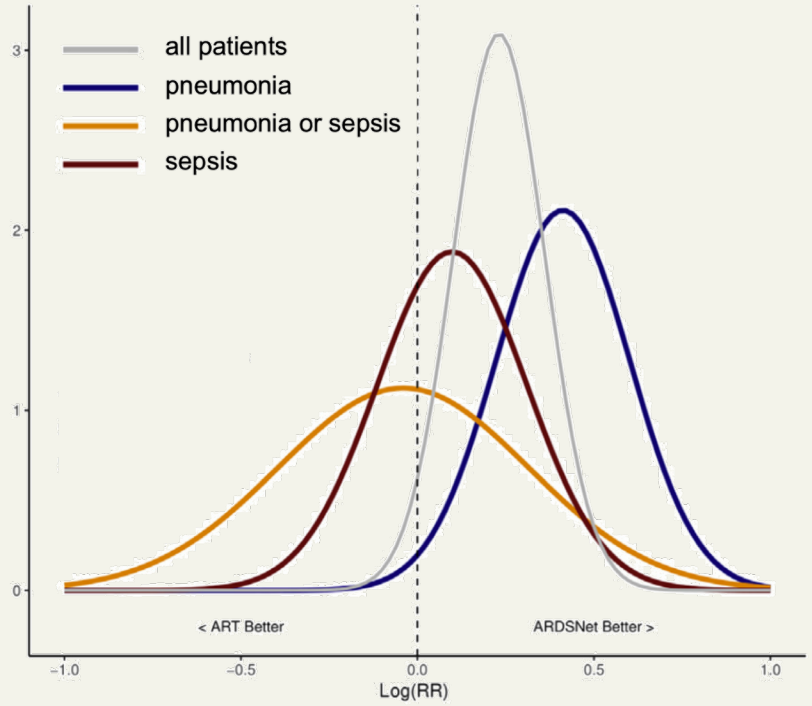
**501** patients
**titrated (high) PEEP [>15 cm $H_2O$] with RM**

**509** patients
**standard (low) PEEP [< 12 cm $H_2O$] without RM**

## OUTCOME OF THE BAYESIAN ANALYSIS

28–day mortality

## FINDINGS




Zampieri F for the ART Investigators. Heterogeneous effects of alveolar recruitment in acute respiratory distress syndrome: a machine learning reanalysis of the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial [*BJA* 2019; **123**:88; 10.1016/j.bja.2019.02.026]

# Conclusions

- more ‘inclusive’ (feasibility)
- may not change the other ‘challenges’ (reliability, validity)
- allows for an ARDS diagnosis in patients receiving HFNO
- lot remains uncertain