ONLINE FIRST

Acute Respiratory Distress Syndrome
The Berlin Definition

The ARDS Definition Task Force*

The acute respiratory distress syndrome (ARDS) was defined in 1994 by the American-European Consensus Conference (AECC); since then, issues regarding the reliability and validity of this definition have emerged. Using a consensus process, a panel of experts convened in 2011 (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine) developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance. A draft definition proposed 3 mutually exclusive categories of ARDS based on degree of hypoxemia: mild (200 mm Hg $<$ Pao_2/Fio_2 $\leq$ 300 mm Hg), moderate (100 mm Hg $<$ Pao_2/Fio_2 $\leq$ 200 mm Hg), and severe (Pao_2/Fio_2 $\leq$ 100 mm Hg) and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance ($\leq$40 mL/cm H_2O), positive end-expiratory pressure ($\geq$10 cm H_2O), and corrected expired volume per minute ($\geq$10 L/min). The draft Berlin Definition was empirically evaluated using patient-level meta-analysis of 4188 patients with ARDS from 4 multicenter clinical data sets and 269 patients with ARDS from 3 single-center data sets containing physiologic information. The 4 ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition. Using the Berlin Definition, stages of mild, moderate, and severe ARDS were associated with increased mortality (27%; 95% CI, 24%-30%; 32%; 95% CI, 29%-34%; and 45%; 95% CI, 42%-48%, respectively; $P < .001$) and increased median duration of mechanical ventilation in survivors (5 days; interquartile [IQR], 2-11; 7 days; IQR, 4-14; and 9 days; IQR, 5-17, respectively; $P < .001$). Compared with the AECC definition, the final Berlin Definition had better predictive validity for mortality, with an area under the receiver operating curve of 0.577 (95% CI, 0.561-0.593) vs 0.536 (95% CI, 0.520-0.553; $P < .001$). This updated and revised Berlin Definition for ARDS addresses a number of the limitations of the AECC definition. The approach of combining consensus discussions with empirical evaluation may serve as a model to create more accurate, evidence-based, critical illness syndrome definitions and to better inform clinical care, research, and health services planning.

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VALID AND RELIABLE DEFINITIONS are essential to conduct epidemiological studies successfully and to facilitate enrollment of a consistent patient phenotype into clinical trials.[1] Clinicians also need such definitions to implement the results of clinical trials, discuss prognosis with families, and plan resource allocation.

Following the initial description of acute respiratory distress syndrome (ARDS) by Ashbaugh et al[2] in 1967, multiple definitions were proposed and used until the 1994 publication of the American-European Consensus Conference (AECC) definition.[3] The AECC defined ARDS as the acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen [Pao_2/Fio_2] $\leq$ 200 mm Hg) with bilateral infiltrates on frontal chest radiograph, with no evidence of left atrial hypertension. A new overarching entity—acute lung injury (ALI)—was also described, using similar criteria but with less severe hypoxemia (Pao_2/Fio_2 $\leq$ 300 mm Hg).[3]

The AECC definition was widely adopted by clinical researchers and clinicians and has advanced the knowledge of ARDS by allowing the acquisition of clinical and epidemiological data, which in turn have led to improvements in the ability to care for patients with ARDS. However, after 18 years of applied research, a number of issues regarding various criteria of the AECC definition have emerged, including a lack of explicit criteria for defining acute, sensitivity of Pao_2/Fio_2 to different ventilator settings, poor reliability of the chest radiograph criterion, and difficulties distinguishing hydrostatic edema (TABLE 1).[4]

For editorial comment see p 2542.

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For these reasons, and because all disease definitions should be reviewed periodically, the European Society of Intensive Care Medicine convened an international expert panel to revise the ARDS definition, with endorsement from the American Thoracic Society and the Society of Critical Care Medicine. The objectives were to update the definition using new data (epidemiological, physiological, and clinical trials) to address the current limitations of the AECC definition and explore other defining variables.

Table 1. The AECC Definition[3]—Limitations and Methods to Address These in the Berlin Definition

	AECC Definition	AECC Limitations	Addressed in Berlin Definition
Timing	Acute onset	No definition of acute[4]	Acute time frame specified
ALI category	All patients with PaO_2/FIO_2 <300 mm Hg	Misinterpreted as PaO_2/FIO_2 = 201-300, leading to confusing ALI/ARDS term	3 Mutually exclusive subgroups of ARDS by severity ALI term removed
Oxygenation	PaO_2/FIO_2 ≤300 mm Hg (regardless of PEEP)	Inconsistency of PaO_2/FIO_2 ratio due to the effect of PEEP and/or FIO_2[5-7]	Minimal PEEP level added across subgroups FIO_2 effect less relevant in severe ARDS group
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Poor interobserver reliability of chest radiograph interpretation[8,9]	Chest radiograph criteria clarified Example radiographs created[a]
PAWP	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	High PAWP and ARDS may coexist[10,11] Poor interobserver reliability of PAWP and clinical assesments of left atrial hypertension[12]	PAWP requirement removed Hydrostatic edema not the primary cause of respiratory failure Clinical vignettes created[a] to help exclude hydrostatic edema
Risk factor	None	Not formally included in definition[4]	Included When none identified, need to objectively rule out hydrostatic edema

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FIO_2, fraction of inspired oxygen; PaO_2, arterial partial pressure of oxygen; PAWP, pulmonary artery wedge pressure; PEEP, positive end-expiratory pressure.
[a]Available on request.

Methods

Consensus Process. Three co-chairs were appointed by the European Society of Intensive Care Medicine, who in turn selected panelists based on their work in the area of ARDS and to ensure geographic representation from both Europe and North America. An overview of the consensus process used by the panel is outlined in the FIGURE. In revising the definition of ARDS, the panel emphasized feasibility, reliability, face validity (ie, how clinicians recognize ARDS), and predictive validity (ie, ability to predict response to therapy, outcomes, or both). In addition, the panel determined that any revision of the definition should be compatible with the AECC definition to facilitate interpretation of previous studies. After initial preparations and an in-person consensus discussion, a draft definition was proposed,[13] which underwent empirical evaluation. The definition was further refined through consensus discussion informed by these empirical data.

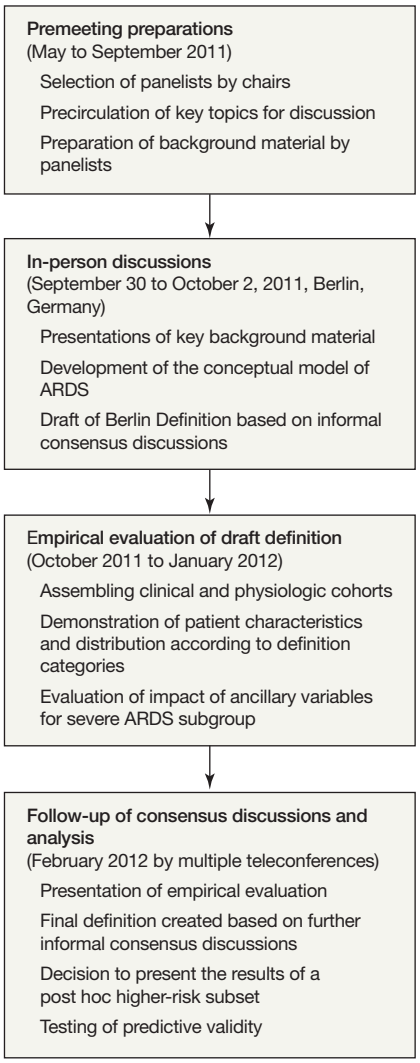
Empirical Evaluation of Draft Definition.

Cohort Assembly. Through the review of the literature presented at the consensus meeting, discussions with other experts, and review of personal files, the panel identified studies that met the following eligibility criteria: (1) large, multicenter prospective cohorts, including consecutive patients or randomized trials, or smaller, single-center prospective studies with unique radiological or physiological data that enrolled adult patients with ALI as defined by AECC; (2) studies collected granular data necessary to apply the individual criteria of both the draft Berlin Definition and the AECC definition; and (3) authors of these original studies were willing to share data and collaborate. The panel identified 7 distinct data sets (4 multicenter clinical studies for the clinical database[14-17] and 3 single-center physiological studies for the physiological database[18-20]) that met these criteria. Further details of these studies are included in the eMethods (http://www.jama.com).

Variables. Studies provided data on hospital or 90-day mortality. Ventilator-free days at 28 days after the diagnosis of ALI were calculated as a composite measure of mortality and duration of mechanical ventilation. Duration of mechanical ventilation in survivors was selected as an indirect marker of severity of lung injury because this outcome is not biased by mortality or decisions related to the withdrawal of life-sustaining treatments.[21] Progression of severity of ARDS within 7 days was assessed using the longitudinal data collected within each cohort. We distinguished patients with more extensive involvement on the frontal chest radiograph (3 or 4 quadrants) from those with the minimal criterion of "bilateral opacities" (2 quadrants).

Static compliance of the respiratory system (C_{RS}) was calculated as tidal volume (mL) divided by plateau pressure (cm H_2O) minus positive end-expiratory pressure (PEEP) (cm H_2O). The corrected expired volume per minute ($\dot{V}E_{CORR}$) was calculated as the measured minute ventilation multiplied by the arterial partial pressure of carbon dioxide ($PaCO_2$) divided by 40 mm Hg.[22] Total lung weight was estimated from quantitative computed tomography (CT) images.[23] Shunt was calculated at one site as previously reported.[24]

Figure. Outline of Consensus Process



ARDS indicates acute respiratory distress syndrome.

Analytic Framework and Statistical Methods. The analytic framework for evaluating the draft Berlin ARDS Definition was to (1) determine the distribution of patient characteristics across the defined severity categories; (2) evaluate the value of proposed ancillary variables (more severe radiographic criterion, higher PEEP levels, static respiratory compliance, and $\dot{V}E_{CORR}$) in defining the severe ARDS subgroup in the draft definition; (3) determine the predictive validity for mortality of the final Berlin Definition; and (4) compare the final Berlin Definition to the AECC definition. In addition, in a post hoc analysis, we sought thresholds for C_{RS} and $\dot{V}E_{CORR}$ that would identify a severe group of patients with ARDS who had more than 50% mortality and include more than 10% of the study population.

We did not evaluate other PaO_2/FIO_2 cutoffs or the requirement of a minimum PEEP level (5 cm H_2O) as they were selected by the panel using face validity criteria and to ensure compatibility with prior definitions. Similarly, we did not explore other variables that might improve predictive validity, such as age and severity of nonpulmonary organ failure, because they were not specific to the definition of ARDS.[25]

To compare the predictive validity of the AECC definition and the Berlin Definition, we used the area under the receiver operating curve (AUROC or C statistic) in logistic regression models of mortality with a dummy variable for the ARDS definition categories.[26] Because this technique requires independent categories to create the dummy variable and the AECC definition for ARDS is a subset of ALI, we could not compare the AECC definition as specified. Therefore, we modified the AECC definition and divided ALI into the independent categories of ALI non-ARDS (200 mm Hg $<$ $PaO_2/FIO_2 \leq$ 300 mm Hg) and ARDS alone ($PaO_2/FIO_2 \leq$ 200 mm Hg). Although the category of ALI non-ARDS is not explicitly described by the AECC, it has been used by many investigators.[27,28]

P values for categorical variables were calculated with the χ^2 test; *P* values for continuous variables were estimated with the *t* test, Mann-Whitney, analysis of variance, or Kruskal-Wallis, depending on the distribution and number of variables. The receiver operating curve statistical analyses were performed by using MedCalc for Windows version 12.1.4.0 (MedCalc Software) and other statistical tests were performed with SAS/STAT for Windows version 9.2 (SAS Institute Inc). Statistical significance was assessed at the 2-sided $P < .05$ level.

Results

Draft Consensus Definition.

The ARDS Conceptual Model. The panel agreed that ARDS is a type of acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (ie, edema, inflammation, hyaline membrane, or hemorrhage).[29]

Draft Definition Criteria. Following 2 days of consensus discussions, the panel proposed a draft definition with 3 mutually exclusive severity categories (mild, moderate, and severe) of ARDS. A set of ancillary variables was proposed to further characterize severe ARDS and these were explicitly specified for further empirical evaluation.[13]

Timing. Most patients with ARDS are identified within 72 hours of recognition of the underlying risk factor, with nearly all patients with ARDS identified within 7 days.[30] Accordingly, for a patient to be defined as having ARDS, the onset must be within 1 week of a known clinical insult or new or worsening respiratory symptoms.

Chest Imaging. The panel retained bilateral opacities consistent with pulmonary edema on the chest radiograph as defining criteria for ARDS, but also explicitly recognized that these findings could be demonstrated on CT scan instead of chest radiograph. More extensive opacities (ie, 3 or 4 quadrants on chest radiograph) were proposed as part of the severe ARDS category and identified for further evaluation.

Origin of Edema. Given the declining use of pulmonary artery catheters and because hydrostatic edema in the form of cardiac failure or fluid overload may coexist with ARDS,[10,11] the pulmonary artery wedge pressure criterion was removed from the defini-

Table 2. Exploration of Proposed Variables to Define Severe ARDS[a]

Severe ARDS Definition	Mild		Moderate		Severe	
	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)	No. (%) of Patients	% Mortality (95% CI)
Consensus panel draft						
Pa_{O_2}/F_{IO_2} ≤100 mm Hg + chest radiograph of 3 or 4 quadrants + PEEP ≥10 cm H_2O + (C_{RS} ≤40 mL/cm H_2O or $\dot{V}E_{CORR}$ ≥10 L/min)	220 (22)	27 (24-30)	2344 (64)	35 (33-36)	507 (14)	45 (40-49)[b]
Consensus panel final						
Pa_{O_2}/F_{IO_2} ≤100 mm Hg	220 (22)	27 (24-30)	1820 (50)	32 (29-34)	1031 (28)	45 (42-48)[b,c]

Abbreviations: ARDS, acute respiratory distress syndrome; C_{RS}, compliance of the respiratory system; F_{IO_2}, fraction of inspired oxygen; Pa_{O_2}, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; $\dot{V}E_{CORR}$, corrected expired volume per minute.

[a] The moderate group includes patients with Pa_{O_2}/F_{IO_2} ≤200 mm Hg and patients with Pa_{O_2}/F_{IO_2} ≤100 mm Hg who do not meet the additional criteria for severe ARDS in the draft definition. All patients are receiving at least 5 cm H_2O PEEP and have bilateral infiltrates on chest radiograph.

[b] $P < .001$ comparing mortality across stages of ARDS (mild, moderate, severe) for draft and final definitions.

[c] $P = .97$ comparing mortality in consensus draft severe ARDS to consensus final severe ARDS definitions.

tion. Patients may qualify as having ARDS as long as they have respiratory failure not fully explained by cardiac failure or fluid overload as judged by the treating physician using all available data. If no ARDS risk factor (eTable 1) is apparent, some objective evaluation (eg, with echocardiography) is required to help eliminate the possibility of hydrostatic edema.

Oxygenation. The term *acute lung injury* as defined by the AECC was removed, due to the perception that clinicians were misusing this term to refer to a subset of patients with less severe hypoxemia rather than its intended use as an inclusive term for all patients with the syndrome. Positive end-expiratory pressure can markedly affect Pa_{O_2}/F_{IO_2}[5,6]; therefore, a minimum level of PEEP (5 cm H_2O), which can be delivered noninvasively in mild ARDS, was included in the draft definition of ARDS. A minimum PEEP level of 10 cm H_2O was proposed and empirically evaluated for the severe ARDS category.

Additional Physiologic Measurements. Compliance of the respiratory system largely reflects the degree of lung volume loss.[2] Increased dead space is common in patients with ARDS and is associated with increased mortality.[24] However, because the measurement of dead space is challenging, the panel chose minute ventilation standardized at a Pa_{CO_2} of 40 mm Hg ($\dot{V}E_{CORR}$ = minute ventilation × Pa_{CO_2}/40) as a surrogate.[22] The draft definition of severe ARDS included the requirement of either a low respiratory system compliance (<40 mL/cm H_2O), a high $\dot{V}E_{CORR}$ (>10 L/min), or both. These variables were identified for further study during the evaluation phase.

The panel considered a number of additional measures to improve specificity and face validity for the increased pulmonary vascular permeability and loss of aerated lung tissue that are the hallmarks of ARDS, including CT scanning, and inflammatory or genetic markers (eTable 2). The most common reasons for exclusion of these measures were lack of routine availability, lack of safety of the measure in critically ill patients, or a lack of demonstrated sensitivity, specificity, or both for use as a defining characteristic for ARDS.

Empirical Evaluation of the Draft Definition.

Patients. A total of 4188 patients in the clinical database had sufficient data to classify as having ARDS by the AECC definition. Of these patients, 518 (12%) could not be classified by the draft Berlin Definition because PEEP was missing or was less than 5 cm H_2O. Patients who could not be classified by the draft Berlin Definition had a mortality rate of 35% (95% CI, 31%-39%), a median (interquartile range [IQR]) of 19 (1-25) ventilator-free days, and a median (IQR) duration of mechanical ventilation in survivors of 4 (2-8) days. These patients were excluded from analyses of the draft Berlin Definition and comparisons between the AECC definition and the draft Berlin Definition.

Compared with patients from the population-based cohorts, patients from clinical trials and the academic centers cohorts were younger, had more severe hypoxemia, and had more opacities on chest radiographs. The cohort of patients from the clinical trials had the lowest mortality, likely reflecting the inclusion and exclusion criteria of the trials.[31] The cohort of patients from academic centers had the highest mortality and the lowest percentage of trauma patients, reflecting the referral population (eTable 3).

There were 269 patients in the physiological database with sufficient data to classify ARDS by the AECC definition, although the numbers of patients in each cohort were small. Patients in the Turin cohort had worse Pa_{O_2}/F_{IO_2} ratios and had higher mortality than the other studies (eTable 4).

Evaluation of Ancillary Variables. The draft Berlin Definition for severe ARDS that included a Pa_{O_2}/F_{IO_2} of 100 mm Hg or less, chest radiograph with 3 or 4 quadrants with opacities, PEEP of at least 10 cm H_2O, and either a C_{RS} of 40 mL/cm H_2O or less or a $\dot{V}E_{CORR}$ of at least 10 L/min identified a smaller set of patients with identical mortality to the simpler severe ARDS category of Pa_{O_2}/F_{IO_2} of 100 mm Hg or less (**TABLE 2**). To address the possibility that the C_{RS} and $\dot{V}E_{CORR}$ thresholds might be different in patients with higher body weight, we evaluated weight-adjusted cutoffs for

these variables in one of the cohorts. There was no significant difference in the predictive validity of the weight-adjusted criteria. The consensus panel reviewed these results and considered the lack of evidence for predictive validity of these ancillary variables and their potential contribution to face validity and construct validity and decided to use the simpler definition for severe ARDS that relied on oxygenation alone.

The Berlin Definition. The final Berlin Definition of ARDS is shown in TABLE 3. Twenty-two percent (95% CI, 21%-24%) of patients met criteria for mild ARDS (which is comparable with the ALI non-ARDS category of the AECC definition; TABLE 4), 50% (95% CI, 48%-51%) of patients met criteria for moderate ARDS, and 28% (95% CI, 27%-30%) of patients met criteria for severe ARDS. Mortality increased with stages of ARDS from mild (27%; 95% CI, 24%-30%) to moderate (32%; 95% CI, 29%-34%) to severe (45%; 95% CI, 42%-48%). Median (IQR) ventilator-free days declined with stages of ARDS from mild (20 [1-25] days) to moderate (16 [0-23] days) to severe (1 [0-20] day). Median (IQR) duration of mechanical ventilation in survivors increased with stages of ARDS from mild (5 [2-11] days) to moderate (7 [4-14] days) to severe (9 [5-17] days).

Using the Berlin Definition, 29% (95% CI, 26%-32%) of patients with mild ARDS at baseline progressed to moderate ARDS and 4% (95% CI, 3%-6%) progressed to severe ARDS within 7 days; and 13% (95% CI, 11%-14%) of patients with moderate ARDS at baseline progressed to severe ARDS within 7 days. All differences between outcome variables across categories of modified AECC (ALI non-ARDS and ARDS alone) and across categories of Berlin Definition (mild, moderate, and severe) were statistically significant ($P<.001$).

Compared with the AECC definition, the final Berlin Definition had better predictive validity for mortality with an AUROC of 0.577 (95% CI, 0.561-0.593) vs 0.536 (95% CI, 0.520-0.553; $P<.001$), with the difference in AUROC of 0.041 (95% CI, 0.030-0.050). To ensure that missing PEEP data in one of the cohorts did not bias the results, the regression analysis was repeated without this cohort and yielded similar results.

The Berlin Definition performed similarly in the physiological database as in the clinical database (TABLE 5, eFigure 1, and eFigure 2). Twenty-five percent (95% CI, 20%-30%) of patients met criteria for mild ARDS, 59% (95% CI, 54%-66%) of patients met criteria for moderate ARDS, and 16% (95% CI, 11%-21%) of patients met criteria for severe ARDS. Mortality increased with stages of ARDS from mild (20%; 95% CI, 11%-31%) to moderate (41%; 95% CI, 33%-49%) to severe (52%; 95% CI, 36%-68%), with $P=.001$ for differences in mortality across stages of ARDS. Median (IQR) ventilator-free days declined with stages of ARDS from mild

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Table 4. Predictive Validity of ARDS Definitions in the Clinical Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	1001 (24) [23-25]	3187 (76) [75-77]	819 (22) [21-24]	1820 (50) [48-51]	1031 (28) [27-30]
Progression in 7 d from mild, No. (%) [95% CI]		336 (34) [31-37]		234 (29) [26-32]	33 (4) [3-6]
Progression in 7 d from moderate, No. (%) [95% CI]					230 (13) [11-14]
Mortality, No. (%) [95% CI][b]	263 (26) [23-29]	1173 (37) [35-38]	220 (27) [24-30]	575 (32) [29-34]	461 (45) [42-48]
Ventilator-free days, median (IQR)[b]	20 (2-25)	12 (0-22)	20 (1-25)	16 (0-23)	1 (0-20)
Duration of mechanical ventilation in survivors, median (IQR), d[b]	5 (2-10)	7 (4-14)	5 (2-11)	7 (4-14)	9 (5-17)

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; Fio_2, fraction of inspired oxygen; IQR, interquartile range; Pao_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.
[a] The definitions are the following for ALI non-ARDS (200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg, regardless of PEEP), ARDS (Pao_2/Fio_2 ≤ 200 mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP ≥5 cm H_2O), moderate Berlin Definition (100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O), and severe Berlin Definition (Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O).
[b] Comparisons of mortality, ventilator-free days, and duration of mechanical ventilation in survivors across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are all statistically significant ($P<.001$).

Table 5. Predictive Validity of ARDS Definitions in the Physiologic Database

	Modified AECC Definition[a]		Berlin Definition ARDS[a]		
	ALI Non-ARDS	ARDS	Mild	Moderate	Severe
No. (%) [95% CI] of patients	66 (25) [19-30]	203 (75) [70-80]	66 (25) [20-30]	161 (59) [54-66]	42 (16) [11-21]
Mortality, No. (%) [95% CI][b]	13 (20) [11-31]	84 (43) [36-50]	13 (20) [11-31]	62 (41) [33-49]	22 (52) [36-68]
Ventilator-free days					
Median (IQR)	8.5 (0-23.5)	0 (0-16.0)	8.5 (0-23.5)	0 (0-16.5)	0 (0-6.5)
Missing, No.	10	26	10	25	1
Duration of mechanical ventilation in survivors, median (IQR), d	6.0 (3.3-20.8)	13.0 (5.0-25.5)	6.0 (3.3-20.8)	12.0 (5.0-19.3)	19.0 (9.0-48.0)
Lung weight, mg[c]					
Mean (SD)	1371 (360.4)	1602 (508.1)	1371 (360.4)	1556 (469.7)	1828 (630.2)
Missing, No.	16	48	16	32	16
Shunt, mean (SD), %[c,d]	21 (21)	32 (13)	21 (12)	29 (11)	40 (16)

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen; IQR, interquartile range; Pa_{O_2}, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure.

[a] The definitions are the following for ALI non-ARDS (200 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 300 mm Hg, regardless of PEEP), ARDS ($Pa_{O_2}/F_{IO_2} \leq$ 200 mm Hg, regardless of PEEP), mild Berlin Definition (200 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 300 mm Hg with PEEP $\geq$5 cm H_2O), moderate Berlin Definition (100 mm Hg $<$ $Pa_{O_2}/F_{IO_2} \leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O), and severe Berlin Definition ($Pa_{O_2}/F_{IO_2} \leq$ 100 mm Hg with PEEP $\geq$5 cm H_2O).

[b] Eight patients are missing in the moderate Berlin Definition ARDS group. $P = .001$ for difference in mortality across Berlin stages of ARDS.

[c] Comparisons of lung weight and shunt across categories of modified AECC (ALI non-ARDS and ARDS) and across categories of Berlin Definition (mild, moderate, and severe) are statistically significant ($P < .001$).

[d] Only available at 1 site.

(8.5 [0-23.5] days) to moderate (0 [0-16.5] days) to severe (0 [0-6.5] days), with $P = .003$ for differences in ventilator-free days across stages of ARDS. Median (IQR) duration of mechanical ventilation in survivors increased with stages of ARDS from mild (6.0 [3.3-20.8] days) to moderate (12.0 [5.0-19.3] days) to severe (19.0 [9.0-48.0] days), with $P = .045$ for differences in duration of mechanical ventilation in survivors across stages of ARDS.

Using the Berlin Definition, stages of mild, moderate, and severe ARDS had increased mean lung weight by CT scan (1371 mg; 95% CI, 1268-1473; 1556 mg; 95% CI, 1474-1638; and 1828 mg; 95% CI, 1573-2082; respectively) and increased mean shunt (21%; 95% CI, 16%-26%; 29%; 95% CI, 26%-32%; and 40%; 95% CI, 31%-48%; respectively). Comparisons of lung weight and shunt (from the single site providing these data) across categories of modified AECC (ALI non-ARDS and ARDS alone) and across categories of Berlin Definition (mild, moderate, and severe) were statistically significant ($P < .001$) (Table 5, eFigure 3, and eFigure 4).

In a post hoc analysis, combining a Pa_{O_2}/F_{IO_2} of 100 mm Hg or less with either a C_{rs} of 20 mL/cm H_2O or less or a $\dot{V}E_{CORR}$ of at least 13 L/min identified a higher-risk subgroup among patients with severe ARDS that included 15% of the entire ARDS population and had a mortality of 52% (95% CI, 48%-56%). Patients with severe ARDS who did not meet the higher-risk subset criteria included 13% of the entire ARDS population and had a mortality rate of 37% (95% CI, 33%-41%). The difference between the mortality of patients with higher-risk severe ARDS and patients with severe ARDS who did not meet these criteria was statistically significant ($P < .001$).

Comment

Developing and disseminating formal definitions for clinical syndromes in critically ill patients are essential for research and clinical practice. Although previous proposals have relied solely on the consensus process, this is to our knowledge the first attempt in critical care to link an international consensus panel endorsed by professional societies with an empirical evaluation.

The draft Berlin Definition classified patients with ARDS into 3 independent categories but relied on ancillary variables (severity of chest radiograph, PEEP $\geq$10 cm H_2O, C_{RS} $\leq$40 mL/cm H_2O, and $\dot{V}E_{CORR}$ $\geq$10 L/min) in addition to oxygenation to define the severe ARDS group. When the ancillary variables selected by the panel were subjected to evaluation, these parameters did not identify a group of patients with higher mortality and were excluded from the final Berlin Definition after further consensus discussion. Without this evaluation, a needlessly complex ARDS definition would have been proposed. However, static respiratory system compliance and an understanding of minute ventilation are important variables for clinicians to consider in managing patients with ARDS, even though those variables were not included as part of the definition.[32]

The Berlin Definition addresses some of the limitations of the AECC definition, including clarification of the exclusion of hydrostatic edema and adding minimum ventilator settings, and provides slight improvement in predictive validity. Our study presents data on the outcomes of patients with ARDS defined according to the Berlin Definition in a large heterogeneous cohort of patients including patients managed with modern approaches to lung protective ventilation. Estimates of the prevalence and clinical outcomes of mild, moderate, and severe ARDS can be assessed from this database for research and health services planning.

Acute respiratory distress syndrome is a heterogeneous syndrome with com-

plex pathology and mechanisms. The proposed definition does not resolve this problem. Investigators may choose to design future trials using 1 or more of the ARDS subgroups as a base study population, which may be further refined using criteria specific to the putative mechanism of action of the intervention (eg, IL-6 levels for an anti–IL-6 trial or more stringent hypoxemia criteria for a study on extracorporeal membrane oxygenation). Furthermore, some variables that were excluded from the Berlin Definition because of current feasibility and lack of data on operational characteristics may become more useful in the future. We anticipate that clinical research using our model of definition development will be used to revise the definition in the future.

There are limitations to our approach. First, although the Berlin Definition had statistically significantly superior predictive validity for mortality compared with the modified AECC definition, the magnitude of this difference and the absolute values of the AUROC are small and would be clinically unimportant if the Berlin Definition was designed as a clinical prediction tool. However, predictive validity for outcome is only one criterion for evaluating a syndrome definition and the purpose of the Berlin Definition is not a prognostication tool.[33] Although the Berlin Definition was developed with a framework including these criteria, we did not empirically evaluate face validity, content validity, reliability, feasibility, or success at identifying patients for clinical trial enrollment.

Second, it is possible that our results are not generalizable because of the data sets we studied. This seems unlikely because patients from a broad range of populations, including clinical trials, academic centers, and community patients, were included in the analyses.

Third, some variables (eg, C_{RS} and PEEP) were missing in some patients in the data sets we used, either due to the mode of mechanical ventilation that precluded their measurement or the practicalities of population-based research. However, bias due to cohort selection or missing data seem unlikely because our results were robust to sensitivity analyses that excluded individual cohorts.

Fourth, it is possible that the ancillary variables did not identify a higher-risk subset because the number of quadrants on the chest radiograph cannot be assessed reliably, PEEP was not used in a predictable fashion, or C_{RS} and $\dot{V}E_{CORR}$ were not accurately measured. However, if this is true, it is likely also to be true in future studies and in clinical practice because the study database was constructed from clinical trial, academic, and community sites reflecting practice in the real world of clinical research. In addition, we evaluated PEEP and C_{RS} as used by clinicians in practice and not as a test of prespecified ventilator settings that may be better than the variables evaluated herein, but may not be practical, particularly in observational cohort studies.[5,6]

Fifth, because our study was not an exercise in developing a prognostic model for ARDS, we only considered the variables and cutoffs proposed by the consensus panel. We could not compare this definition directly to the AECC definition because the categories of that definition overlap. It is possible that the outcomes as well as the relative proportion of patients within each category of ARDS will change if the underlying epidemiology of the syndrome evolves due to changes in clinical practice or risk factors.[34] This is particularly true for the post hoc higher-risk subset reported, for which the cut points were derived from the data sets.

Conclusion

In conclusion, we developed a consensus draft definition for ARDS with an international panel using a framework that focused on feasibility, reliability, and validity. We tested that definition using empirical data on clinical outcome, radiographic findings, and physiological measures from 2 large databases constructed from 7 contributing sources to assess the predictive value of ancillary variables, refine the draft definition, and compare the predictive validity of the definition to the existing AECC definition. This approach for developing the Berlin Definition for ARDS may serve as an example for linking consensus definition activities with empirical research to better inform clinical care, research, and health services planning.

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