# Lung Recruitability Is Better Estimated According to the Berlin Definition of Acute Respiratory Distress Syndrome at Standard 5 cm $H_2O$ Rather Than Higher Positive End-Expiratory Pressure: A Retrospective Cohort Study*

Pietro Caironi, MD[1,2]; Eleonora Carlesso, MSc[1]; Massimo Cressoni, MD[1]; Davide Chiumello, MD[2]; Onner Moerer, MD[3]; Chiara Chiurazzi, MD[1]; Matteo Brioni, MD[1]; Nicola Bottino, MD[2]; Marco Lazzerini, MD[4]; Guillermo Bugedo, MD[5]; Michael Quintel, MD[3]; V. Marco Ranieri, MD[6]; Luciano Gattinoni, MD, FRCP[1,2]

***See also p. 913.**

[1]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy.

[2]Dipartimento di Anestesia, Rianimazione e Terapia del Dolore, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy.

[3]Department of Anesthesiology, Emergency and Intensive Care Medicine, Georg-August University of Göttingen, Göttingen, Germany.

[4]Dipartimento di Radiologia, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy.

[5]Departmentos de Anestesiologia y Medicina Intensiva, Facultad de Medicina, Pontificia, Universidad Catolica de Chile, Santiago, Chile.

[6]Dipartimento di Anestesia, Azienda Ospedaliera San Giovanni Battista-Molinette, Università degli Studi di Torino, Turin, Italy.

Drs. Caironi, Carlesso, Chiumello, and Gattinoni contributed to conception and design of the study. Drs. Carlesso, Cressoni, Chiumello, Moerer, Chiurazzi, Brioni, Bottino, Lazzerini, Bugedo, Quintel, and Ranieri contributed to acquisition of data. Drs. Caironi, Carlesso, Cressoni, Chiurazzi, Brioni, Lazzerini, and Gattinoni contributed to analysis and interpretation of data. Drs. Caironi, Carlesso, and Gattinoni contributed to drafting of the article. Drs. Caironi, Carlesso, Cressoni, Chiumello, Moerer, Bottino, Bugedo, Quintel, Ranieri, and Gattinoni contributed to critical revision of the article for important intellectual content. Drs. Caironi and Carlesso contributed to statistical analysis.

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Address requests for reprints to: Pietro Caironi, MD, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via F. Sforza 35, 20122 Milano, Italy. E-mail: pietro.caironi@unimi.it

**Objectives:** The Berlin definition of acute respiratory distress syndrome has introduced three classes of severity according to $Pa_{O_2}/F_{IO_2}$ thresholds. The level of positive end-expiratory pressure applied may greatly affect $Pa_{O_2}/F_{IO_2}$, thereby masking acute respiratory distress syndrome severity, which should reflect the underlying lung injury (lung edema and recruitability). We hypothesized that the assessment of acute respiratory distress syndrome severity at standardized low positive end-expiratory pressure may improve the association between the underlying lung injury, as detected by CT, and $Pa_{O_2}/F_{IO_2}$-derived severity.
**Design:** Retrospective analysis.
**Setting:** Four university hospitals (Italy, Germany, and Chile).
**Patients:** One hundred forty-eight patients with acute lung injury or acute respiratory distress syndrome according to the American-European Consensus Conference criteria.
**Interventions:** Patients underwent a three-step ventilator protocol (at clinical, 5 cm $H_2O$, or 15 cm $H_2O$ positive end-expiratory pressure). Whole-lung CT scans were obtained at 5 and 45 cm $H_2O$ airway pressure.
**Measurements and Main Results:** Nine patients did not fulfill acute respiratory distress syndrome criteria of the novel Berlin definition. Patients were then classified according to $Pa_{O_2}/F_{IO_2}$ assessed at clinical, 5 cm $H_2O$, or 15 cm $H_2O$ positive end-expiratory pressure. At clinical positive end-expiratory pressure (11 ± 3 cm $H_2O$), patients with severe acute respiratory distress syndrome had a greater lung tissue weight and recruitability than patients with mild or moderate acute respiratory distress syndrome ($p < 0.001$). At 5 cm $H_2O$, 54% of patients with mild acute

respiratory distress syndrome at clinical positive end-expiratory pressure were reclassified to either moderate or severe acute respiratory distress syndrome. In these patients, lung recruitability and clinical positive end-expiratory pressure were higher than in patients who remained in the mild subgroup ($p < 0.05$). When patients were classified at 5 cm $H_2O$, but not at clinical or 15 cm $H_2O$, lung recruitability linearly increases with acute respiratory distress syndrome severity (5% [2–12%] vs 12% [7–18%] vs 23% [12–30%], respectively, $p < 0.001$). The potentially recruitable lung was the only CT-derived variable independently associated with ICU mortality ($p = 0.007$).

**Conclusions:** The Berlin definition of acute respiratory distress syndrome assessed at 5 cm $H_2O$ allows a better evaluation of lung recruitability and edema than at higher positive end-expiratory pressure clinically set. (*Crit Care Med* 2015; 43:781–790)

**Key Words:** acute respiratory distress syndrome; computed tomography; mechanical ventilation; positive end-expiratory pressure

The acute respiratory distress syndrome (ARDS) consists of a set of symptoms of acute respiratory failure, originating from several stimuli, but sharing a common pathological feature, that is, inflammatory pulmonary edema (1). Its definition has been recently reviewed in Berlin by a panel of experts (2), who proposed three mutually exclusive ARDS categories according to the degree of hypoxemia: mild ($Pa{O_2}/F{IO_2}$ between 201 and 300 mm Hg), moderate ($Pa{O_2}/F{IO_2}$ between 101 and 200 mm Hg), and severe ($Pa{O_2}/F{IO_2}$ of 100 mm Hg or less). In a large patient-level meta-analysis, these categories differed in outcome, impairment of pulmonary pathophysiology, lung weight, and histology (2–4). Of note, despite the well-known influence of positive end-expiratory pressure (PEEP) on oxygenation (5–7), the Berlin definition did not include any standardization of its level when assessing $Pa{O_2}/F{IO_2}$, except for a minimal level of 5 cm $H_2O$.

In the past years, CT has become an important tool to assess ARDS severity through the study of lung edema and aeration (8, 9). In a cohort of patients with ARDS, we have identified lung recruitability as a key feature of ARDS lung morphology (10). The percentage of potentially recruitable lung appeared widely variable among patients, strictly associated with the overall lung injury severity, and an independent risk factor for death. Furthermore, our group and others have shown that lung recruitability affects the efficacy of ventilator strategies usually reserved to the most severe patients, such as higher PEEP (11, 12) or prone positioning (13-15), as characterized by possible risks (16, 17). Therefore, the assessment of lung edema and recruitability may be crucial for a correct ventilator setting and a full risk stratification of patients with ARDS.

Since lung recruitability affects $Pa{O_2}/F{IO_2}$ variation in response to the PEEP applied (18, 19), and the level of PEEP, per se, may influence the associated $Pa{O_2}/F{IO_2}$, we reasoned that an assessment of ARDS severity at standardized low PEEP might lead to a more accurate match between $Pa{O_2}/F{IO_2}$-derived and CT-derived severity. To verify this hypothesis, we retrospectively analyzed a large cohort of patients with ARDS, aiming at describing lung edema and recruitability according to the Berlin definition and at elucidating whether the assessment of $Pa{O_2}/F{IO_2}$ at standardized PEEP (5 or 15 cm $H_2O$) allows a more accurate description of ARDS severity as compared to its clinical assessment.

## MATERIALS AND METHODS

### Study Population

We retrospectively analyzed 148 patients with acute lung injury or ARDS according to the American-European Consensus Conference (AECC) criteria (20), previously enrolled in four clinical trials (10, 21, 22) (one of which still ongoing, NCT00759590), from four university hospitals in Italy, Germany, and Chile. Each study was approved by the local institutional review board, and informed consent was obtained (**Supplemental Digital Content 1**, http://links.lww.com/CCM/B141). We reviewed each patient's medical chart to confirm ARDS diagnosis according to the Berlin definition (2), including: 1) an onset within 1 week of a known clinical insult or new or worsening respiratory symptoms; 2) bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules; 3) acute respiratory failure not fully explained by cardiac failure or fluid overload; and 4) a clinical PEEP of at least 5 cm $H_2O$.

### Study Design

Although study protocols were different, each patient always underwent the following phases, applied at ICU admission (in case the patient was referred from another center) or after diagnosis, under sedation and paralysis: 1) a baseline period, in which the ventilator setting was applied by the attending physician, and in which a clinical PEEP was set and 2) a "PEEP test," in which two PEEP levels (5 and 15 cm $H_2O$) were randomly applied for 20 minutes, keeping $F{IO_2}$, tidal volume, and inspiratory to expiratory ratio unmodified. Before the application of each PEEP level (both the PEEP clinically applied as well as 5 and 15 cm $H_2O$), a recruitment maneuver was performed by applying two minutes of pressure-controlled ventilation, at 45 cm $H_2O$ inspiratory pressure, 5 cm $H_2O$ PEEP, 10 breaths/min respiratory rate, and 1:1 inspiratory to expiratory ratio (10). At the end of each 20-minute period, respiratory physiological variables and hemodynamics were recorded. Patients were assigned to a severity category according to the Berlin definition (2) (mild, moderate, or severe ARDS). As each patient was characterized by three different $Pa{O_2}/F{IO_2}$ ratios (at clinical, 5 cm $H_2O$, or 15 cm $H_2O$ PEEP), three classifications were applied.

### CT-Scan Analysis

After the "PEEP test," patients underwent whole-lung CT scanning at end-expiratory 5 cm $H_2O$ PEEP and at end-inspiratory 45 cm $H_2O$ airway pressure. Both CT scans were obtained, respectively, during and end-expiratory and end-inspiratory pauses (ranging from 15 to 25 s). Each cross-sectional image was processed with a custom-designed software, and CT-derived variables were computed, as previously described (10, 23) (Supplemental Digital Content 1, http://links.lww.com/CCM/B141). Briefly, assuming the specific weight of air-free lung tissue equal to 1, we computed the total lung tissue weight, based on the physical density of the lung expressed in Hounsfield units (HU). Subsequently, based on the frequency distribution of the physical density of each voxel, we computed tissue weights of lung compartments according to their degree of aeration: nonaerated (from +100 HU to –100 HU), poorly aerated (from –100 HU to –500 HU), normally aerated (from –500 HU to –900 HU), and hyperinflated (from –900 HU to –1000 HU). The potentially recruitable lung, defined as the difference between nonaerated lung tissue weight at end-expiratory 5 cm $H_2O$ and end-inspiratory 45 cm $H_2O$ airway pressure, was expressed as percentage of the total lung tissue weight.

### Statistical Analysis

Results are presented as mean ± SD, median (interquartile range), or hazard ratio and 95% CI, as appropriate. Comparisons of prestudy, physiological, and CT-derived variables were performed by one-way analysis of variance (ANOVA), the Kruskal-Wallis test, or the chi-square test, as appropriate. Post hoc analysis was performed by Bonferroni-Dunn test. Predictive validity of ARDS definitions for ICU mortality was evaluated by comparing areas under the receiver operating curve (AUROC), with the DeLong, DeLong, and Clarke-Pearson method (24). The association between both CT-derived variables and $Pa_{O_2}/F_{IO_2}$ ratios with ICU survival was first assessed with univariate Cox proportional hazard models. Cox multivariable models were used to establish their independent prognostic value, after adjustment for clinically relevant variables set a priori: Simplified Acute Physiology Score II score, age, normalized minute ventilation, and days of mechanical ventilation before the study. The SAS statistical software 9.2 (SAS Institute, Cary, NC) and SigmaPlot 11.0 (Systat Software, San Jose, CA) were used. Statistical significance was defined as a *p* value less than 0.05.

**TABLE 1. Baseline Characteristics of the Study Population**

| Characteristics | Mild (*n* = 52) | Moderate (*n* = 76) | Severe (*n* = 11) | *p*[a] |
|---|---|---|---|---|
| Age, yr | 63 [47–73] | 62 [50–71] | 65 [45–76] | 0.96 |
| Female sex, *n* (%) | 13 (25) | 26 (34) | 4 (36) | 0.50 |
| Body mass index, kg/m$^2$ | 26 ± 4 | 27 ± 7 | 23 ± 4 | 0.07 |
| Simplified Acute Physiology Score II score | 40 [32–47] | 40 [32–52] | 53 [43–63][b,c] | 0.03 |
| Tidal volume, mL/kg predicted body weight | 8.4 ± 1.6 | 8.3 ± 2.0 | 7.1 ± 1.7 | 0.12 |
| Minute ventilation, L/min | 9.2 ± 2.7 | 9.0 ± 2.6 | 11.0 ± 3.0 | 0.10 |
| Respiratory rate, breaths/min | 17 ± 6 | 17 ± 5 | 22 ± 7 | 0.07 |
| Positive end-expiratory pressure, cm $H_2O$ | 11.3 ± 3.1 | 11.0 ± 2.8 | 10.4 ± 4.2 | 0.71 |
| Plateau pressure, cm $H_2O$[d] | 23 ± 4 | 25 ± 4 | 27 ± 5 | 0.03 |
| Respiratory system Compliance, mL/cm $H_2O$[d] | 50 [38–62] | 35 [31–46][b] | 30 [23–39][b] | < 0.001 |
| $Pa_{O_2}/F_{IO_2}$, mm Hg | 233 ± 22 | 159 ± 26[b] | 79 ± 13[b,c] | < 0.001 |
| $F_{IO_2}$, % | 43 ± 6 | 52 ± 10[b] | 85 ± 15[b,c] | < 0.001 |
| $Pa_{O_2}$, mm Hg | 99 ± 16 | 81 ± 15[b] | 66 ± 11[b,c] | < 0.001 |
| $Pa_{CO_2}$, mm Hg | 39 ± 7 | 43 ± 9[b] | 49 ± 12[b] | < 0.001 |
| Arterial pH[e] | 7.41 ± 0.06 | 7.40 ± 0.07 | 7.35 ± 0.08[b,c] | 0.03 |
| Days of ventilation before study | 3 [2–6] | 4 [2–8] | 2 [1–7] | 0.43 |
| Cause of lung injury, *n* (%) | | | | 0.44 |
| Pneumonia | 19 (37) | 33 (43) | 8 (73) | |
| Sepsis | 18 (35) | 19 (25) | 1 (9) | |
| Aspiration | 3 (6) | 8 (11) | 0 (0) | |
| Trauma | 3 (6) | 6 (8) | 1 (9) | |
| Other | 9 (17) | 10 (13) | 1 (9) | |

[a] *p* values refer to one-way analysis of variance (ANOVA) with post hoc all pairwise multiple comparison procedures (Bonferroni *t* test), Kruskal-Wallis one-way ANOVA on Ranks with post hoc pairwise multiple comparison procedures (Dunn method), or chi-square test as appropriate.

[b] $p < 0.05$ versus patients with mild acute respiratory distress syndrome (ARDS).

[c] $p < 0.05$ versus patients with moderate ARDS.

[d] Data were available for 122 patients (48 patients with mild, 64 with moderate, and 10 with severe ARDS).

[e] Data were available for 137 patients (52 patients with mild, 74 with moderate, and 11 with severe ARDS).

Data are presented as mean ± SD, median [interquartile range], or *n* (%), as appropriate.

**TABLE 2. Lung Edema and Aeration, Recruitability, and ICU Mortality according to the Berlin Definition Applied at Clinical, 5 cm $H_2O$, or 15 cm $H_2O$ Positive End-Expiratory Pressure**

| | | Acute Respiratory Distress Syndrome Severity | | | |
|---|---|---|---|---|---|
| Characteristics | Classification | Mild | Moderate | Severe | $p$[a] |
| Patients, $n$ (%) | Clinical | 52 (37) | 76 (55) | 11 (8) | – |
| | 5 cm $H_2O$ | 27 (19) | 92 (67) | 20 (14) | – |
| | 15 cm $H_2O$ | 52 (42) | 68 (54) | 5 (4.0) | – |
| Clinical positive end-expiratory pressure, cm $H_2O$ | Clinical | 11.3 ± 3.1 | 11.0 ± 2.8 | 10.4 ± 4.2 | 0.71 |
| | 5 cm $H_2O$ | 9.9 ± 2.2 | 10.9 ± 2.9 | 13.3 ± 3.4[b,c] | < 0.001 |
| | 15 cm $H_2O$ | 10.9 ± 2.7 | 11.4 ± 3.0 | 13.6 ± 4.2 | 0.31 |
| Total lung tissue, g | Clinical | 1,289 [1,125–1,496] | 1,427 [1,131–1,691] | 1,686 [1,501–2,502][b,c] | 0.004 |
| | 5 cm $H_2O$ | 1,219 [1,075–1,471] | 1,378 [1,125–1,583] | 1,893 [1,577–2,234][b,c] | < 0.001 |
| | 15 cm $H_2O$ | 1,293 [1,123–1,498] | 1,434 [1,168–1,893] | 1,686 [1,618–1,751] | 0.02 |
| Hyperinflated lung tissue, g | Clinical | 0.5 [0.1–2.1] | 0.2 [0.0–3.5] | 0.2 [0.0–3.0] | 0.59 |
| | 5 cm $H_2O$ | 0.5 [0.0–2.1] | 0.3 [0.0–4.2] | 0.3 [0.0–2.7] | 0.90 |
| | 15 cm $H_2O$ | 0.3 [0.0–1.8] | 0.4 [0.1–4.3] | 0.0 [0.0–3.0] | 0.28 |
| Normally aerated lung tissue, g | Clinical | 400 [297–522] | 338 [244–475][b] | 232 [124–503][b] | 0.006 |
| | 5 cm $H_2O$ | 455 [334–566] | 349 [252–497][b] | 249 [188–420][b] | 0.002 |
| | 15 cm $H_2O$ | 366 [288–492] | 326 [244–506] | 232 [187–253] | 0.11 |
| Poorly aerated lung tissue, g | Clinical | 389 [302–474] | 377 [276–643] | 524 [327–853] | 0.10 |
| | 5 cm $H_2O$ | 336 [241–423] | 418 [284–569] | 685 [337–868][b,c] | 0.002 |
| | 15 cm $H_2O$ | 392 [315–485] | 399 [264–699] | 347 [327–769] | 0.76 |
| Nonaerated lung tissue, g | Clinical | 445 [350–580] | 511 [360–849] | 1,153 [661–1,293][b,c] | < 0.001 |
| | 5 cm $H_2O$ | 405 [336–503] | 502 [348–701] | 961 [579–1,376][b,c] | < 0.001 |
| | 15 cm $H_2O$ | 431 [336–633] | 576 [388–863] | 1,217 [1,031–1,282] | 0.004 |
| Recruitable lung tissue, g[d] | Clinical | 131 [52–219] | 168 [88–306] | 408 [184–706][b,c] | < 0.001 |
| | 5 cm $H_2O$ | 62 [26–164] | 164 [84–279][b] | 431 [180–633][b,c] | < 0.001 |
| | 15 cm $H_2O$ | 140 [60–245] | 168 [88–336] | 454 [408–706] | 0.004 |
| Potentially recruitable lung, %[d] | Clinical | 10 [4–17] | 12 [8–19] | 23 [17–29][b,c] | 0.003 |
| | 5 cm $H_2O$ | 5 [2–12] | 12 [7–18][b] | 23 [12–30][b,c] | < 0.001 |
| | 15 cm $H_2O$ | 11 [5–17] | 12 [8–19] | 26 [24–26] | 0.003 |
| Higher potentially recruitable lung, $n$ (%)[e] | Clinical | 26 (53) | 46 (73) | 9 (82) | 0.18 |
| | 5 cm $H_2O$ | 10 (40) | 54 (61) | 17 (85) | 0.009 |
| | 15 cm $H_2O$ | 29 (58) | 42 (64) | 5 (100) | 0.18 |
| ICU Mortality, $n$ (%) | Clinical | 12 (23) | 31 (41) | 7 (64) | 0.02 |
| | 5 cm $H_2O$ | 7 (26) | 29 (32) | 14 (70) | 0.002 |
| | 15 cm $H_2O$ | 16 (31) | 27 (40) | 4 (80) | 0.08 |

[a] $p$ values refer to one-way analysis of variance (ANOVA) with post hoc all pairwise multiple comparison procedures (Bonferroni $t$ test), Kruskal-Wallis one-way ANOVA on Ranks with post hoc pairwise multiple comparison procedures (Dunn method), or chi-square test as appropriate.

[b] $p < 0.05$ versus patients with mild acute respiratory distress syndrome (ARDS).

[c] $p < 0.05$ versus patients with moderate ARDS.

[d] Data were available for 133 patients evaluated either at clinical positive end-expiratory pressure (PEEP) (49 patients with mild, 73 with moderate, 11 with severe ARDS) or at 5 cm $H_2O$ PEEP (25 patients with mild, 88 with moderate, 20 with severe ARDS) and for 121 patients evaluated at 15 cm $H_2O$ PEEP (50 patients with mild, 66 with moderate, 5 with severe ARDS).

[e] A threshold value of 9% of potentially recruitable lung was applied to define patients with a higher potentially recruitable lung (10).

Data are presented as mean ± SD, median [interquartile range], or $n$ (%), as appropriate. Findings related to lung functional anatomy were assessed by CT scanning performed at 5 cm $H_2O$ PEEP, assumed as standard baseline conditions. Clinical PEEP denoted the PEEP level clinical applied at the beginning of the study. Analyses at 15 cm $H_2O$ PEEP were performed excluding patients who lost $Pa_{O_2}/F_{IO_2}$ threshold for ARDS definition ($n = 13$). Data at 15 cm $H_2O$ were missing for one patient.

Dashes signify that no statistical analysis for comparison between groups has been performed.

## RESULTS

### CT-Lung Injury Severity and Recruitability at Clinical PEEP

Nine of 148 patients did not fulfill the criteria of ARDS Berlin definition and were excluded from the analysis. Among those included, 52 were classified as affected by mild (37%), 76 by moderate (55%), and 11 by severe ARDS (8%). The most relevant respiratory physiological variables, that is, respiratory system compliance, $Pa{O_2}/F{IO_2}$, and $Pa{CO_2}$, deteriorated from mild to severe ARDS ($p < 0.001$ for all, one-way ANOVA; **Table E1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B141) (**Table 1**). Similarly, patients with severe ARDS had a greater lung tissue weight ($p = 0.004$), amount of nonaerated lung tissue ($p < 0.001$), and potential for lung recruitment compared with those with either mild or moderate ARDS ($p = 0.003$; **Fig. E1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B141) (**Table 2**). No differences were observed between patients with mild or moderate ARDS.

### ARDS Severity at Different PEEP

**Figure 1** illustrates the effects of changing PEEP on the classification of ARDS severity, moving from the PEEP clinically applied (11 ± 3 cm $H_2O$) to 5 cm $H_2O$. Out of the 52 patients with mild ARDS at clinical PEEP (**Fig. 1*A***), 26 patients were reassigned to moderate, whereas two to severe ARDS when classified at 5 cm $H_2O$ PEEP. Similarly, out of the 76 patients with moderate ARDS at clinical PEEP (**Fig. 1*B***), two patients were reassigned to mild, whereas 12 to severe ARDS at 5 cm $H_2O$ PEEP. Finally, out of the 11 patients with severe ARDS at clinical PEEP (**Fig. 1*C***), four patients were reassigned to moderate, whereas one to mild ARDS at 5 cm $H_2O$ PEEP. Similar findings were observed when PEEP was changed to 15 cm $H_2O$ (**Fig. E2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B141). Out of the 52 patients with mild ARDS at clinical PEEP, 10 patients presented, at 15 cm $H_2O$ PEEP, a $Pa{O_2}/F{IO_2}$ greater than the threshold value for ARDS definition, whereas eight were reassigned to moderate ARDS. Out of the 76 patients with moderate ARDS, at 15 cm $H_2O$ PEEP, three patients lost $Pa{O_2}/F{IO_2}$ criteria for ARDS definition, 15 were reassigned to mild, and one to severe ARDS. Of note, out of the 11 patients with severe ARDS at clinical PEEP, only four remained in this category at 15 cm $H_2O$ PEEP, whereas three were reassigned to moderate and four to mild ARDS.

Among patients with mild ARDS, those reassigned to moderate ARDS at 5 cm $H_2O$ PEEP had a similar lung weight ($p = 1.00$), but a potentially recruitable lung which tended to be greater than that of patients remaining within the mild ARDS category ($p = 0.06$) (**Table 3**). In the former group, the PEEP clinically applied was higher than that of the latter group ($p < 0.001$), but associated with similar $Pa{O_2}/F{IO_2}$ (239 ± 24 vs 229 ± 19 mm Hg; $p = 0.28$). Similarly, the two patients with mild ARDS reassigned to severe ARDS were clinically treated with a higher PEEP level ($p = 0.004$), as compared to those remaining within the mild ARDS category, and presented an almost five-fold higher percentage of potentially recruitable lung ($p = 0.01$) (**Fig. 2**). Similar findings were observed in patients with either moderate or severe ARDS (Table 3).

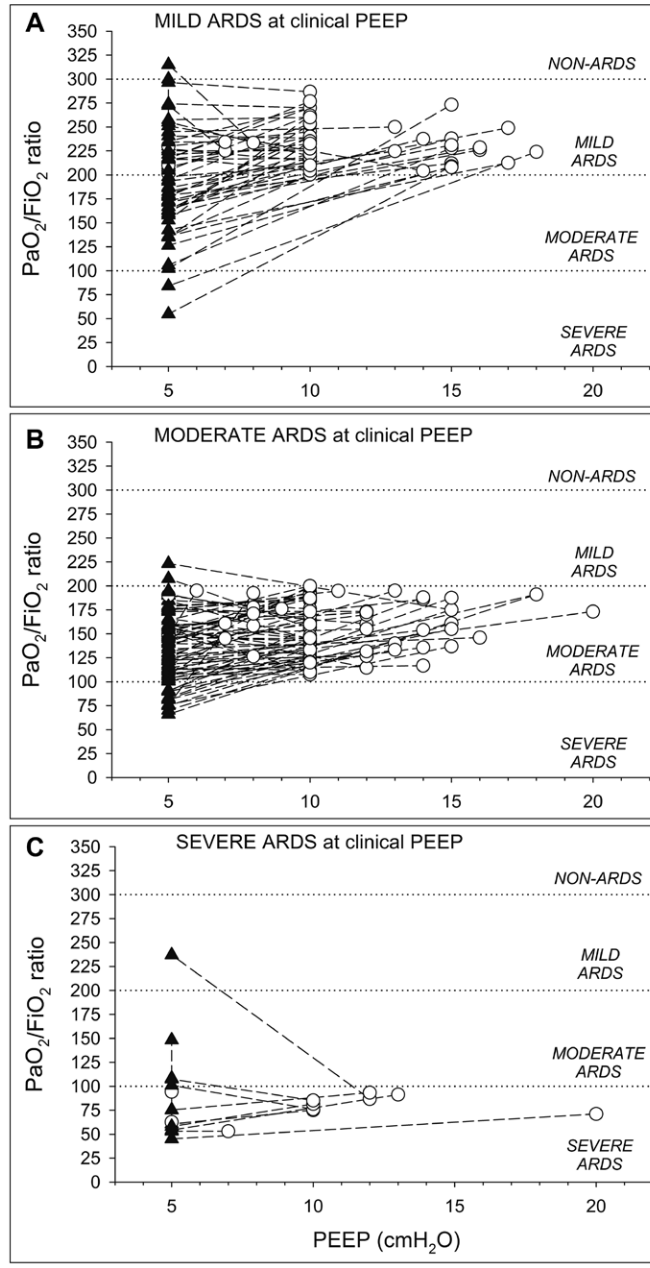


**Figure 1.** Effects of changing positive end-expiratory pressure (PEEP) from clinical value to a standard value of 5 cm $H_2O$ on $Pa{O_2}/F{IO_2}$ in individual patients classified as affected by mild (**A**), moderate (**B**), and severe (**C**) acute respiratory distress syndrome (ARDS) at clinical PEEP. *White dots* represent $Pa{O_2}/F{IO_2}$ values at clinical PEEP, *black triangles* represent $Pa{O_2}/F{IO_2}$ values at 5 cm $H_2O$ PEEP. *Dashed gray lines* represent the different $Pa{O_2}/F{IO_2}$ thresholds for ARDS classifications according to the Berlin definition. As shown, the change of PEEP from its clinical value to standard 5 cm $H_2O$ led to a wide reclassification of patients in each category of ARDS severity. Of note, one patient with mild ARDS at clinical PEEP who lost $Pa{O_2}/F{IO_2}$ criteria for ARDS after applying 5 cm $H_2O$ PEEP, for simplicity, was included in the analysis in the mild ARDS category even at 5 cm $H_2O$ PEEP.

When the Berlin definition was assessed at either 5 or 15 cm $H_2O$ PEEP, the main CT-derived variables defining lung injury severity deteriorated similarly from mild to severe ARDS. Patients with severe ARDS presented a greater total lung tissue weight ($p < 0.001$ and $p = 0.02$, respectively), amount of nonaerated lung tissue ($p < 0.001$ and $p = 0.004$), and percentage of potentially recruitable lung ($p < 0.001$ and $p = 0.003$) (Table 2) compared with those with mild or moderate ARDS. Nonetheless, when the Berlin definition was applied at 5 cm $H_2O$ PEEP, the potential for lung recruitment sharply increased moving from each ARDS category, being double in patients with moderate ($p = 0.007$) and three-fold in those with severe ($p < 0.001$) compared with patients with mild ARDS (**Fig. 3**).

### Subgroup Analysis of Moderate ARDS

Based on the variability of the potentially recruitable lung observed in patients with moderate ARDS even at 5 cm $H_2O$ PEEP, we further divided this subgroup into two categories: moderate-mild ARDS ($PaO_2/FIO_2$ between 150 and 199 mm Hg) and moderate-severe ARDS ($PaO_2/FIO_2$ between 101 and 149 mm Hg). Patients with moderate-severe ARDS had a greater potential for lung recruitment (16% [8–21%] vs 9% [6–16%]; $p = 0.009$), total lung tissue weight (1,498 g [1,289–1,772 g] vs 1,214 g [1,061–1,440 g]; $p < 0.001$), and amount of nonaerated lung tissue (595 g [427–901 g] vs 395 g [317–532 g]; $p < 0.001$) compared with those with moderate-mild ARDS. Furthermore, when evaluating lung injury severity along the four ARDS categories, no differences were ever observed between patients with mild or moderate-mild ARDS. By contrast, the majority of the CT-derived and physiological respiratory variables progressively deteriorated from patients with moderate-mild to those with severe

**TABLE 3. Clinical Positive End-Expiratory Pressure, Lung Functional Anatomy, and Recruitability According to the Agreement or the Modification of Acute Respiratory Distress Syndrome Severity Class of the Berlin Definition Applied at Either Clinical or 5 cm $H_2O$ Positive End-Expiratory Pressure**

| ARDS Severity at Clinical PEEP | Characteristics | ARDS Severity at 5 cm $H_2O$ PEEP | | | |
|---|---|---|---|---|---|
| | | Mild | Moderate | Severe | $p$[a] |
| Mild ARDS ($n$ = 52) | Patients, $n$ (%) | 24 | 26 | 2 | < 0.001 |
| | Clinical PEEP, cm $H_2O$ | 9.5 ± 2.0 | 12.4 ± 3.1[b] | 16.5 ± 2.1[b] | < 0.001 |
| | Total lung tissue, g | 1,273 [1,086–1,472] | 1,280 [1,159–1,498] | 2,479 [2,286–2,672][b] | 0.04 |
| | Nonaerated lung tissue, g | 409 [346–509] | 479 [353–564] | 1,641 [1,499–1,784][b] | 0.05 |
| | Recruitable lung tissue , g[c] | 62 [23–164] | 171 [104–233][b] | 884 [746–1,022][b] | 0.002 |
| | Potentially recruitable lung, %[c] | 5 [2–12] | 12 [6–17] | 35 [33–38][b] | 0.004 |
| Moderate ARDS ($n$ = 76) | Patients, $n$ (%) | 2 | 62 | 12 | < 0.001 |
| | Clinical PEEP, cm $H_2O$ | 12.5 ± 3.5 | 10.5 ± 2.5 | 13.4 ± 2.8[d] | 0.002 |
| | Total lung tissue, g | 1,141 [1,119–1,164] | 1,391 [1,087–1,627] | 1,802 [1,401–2,039][d] | 0.02 |
| | Nonaerated lung tissue, g | 392 [336–449] | 499 [341–823] | 658 [512–1,054] | 0.12 |
| | Recruitable lung tissue, g[c] | 61 [28–94] | 159 [77–288] | 212 [168–470] | 0.04 |
| | Potentially recruitable lung, %[c] | 5 [2–8] | 12 [7–18] | 13 [9–24] | 0.14 |
| Severe ARDS ($n$ = 11) | Patients, $n$ (%) | 1 | 4 | 6 | 0.18 |
| | Clinical PEEP, cm $H_2O$ | 12.0 ± 0.0 | 7.5 ± 2.9 | 12.0 ± 4.4 | 0.14 |
| | Total lung tissue, g | 1,024 [1,024–1,024] | 1,656 [1,495–2,156] | 1,934 [1,618–3,252] | 0.18 |
| | Nonaerated lung tissue, g | 281 [281–281] | 989 [736–1,223] | 1,269 [1,031–1,471] | 0.18 |
| | Recruitable lung tissue, g | 176 [176–176] | 249 [135–626] | 630 [408–706] | 0.21 |
| | Potentially recruitable lung, % | 17 [17–17] | 14 [7–36] | 25 [23–29] | 0.34 |

ARDS = acute respiratory distress syndrome, PEEP = positive end-expiratory pressure.

[a]$p$ values refer to one-way analysis of variance (ANOVA) with post hoc all pairwise multiple comparison procedures (Bonferroni $t$ test), Kruskal-Wallis one-way ANOVA on Ranks with post hoc pairwise multiple comparison procedures (Dunn method), or chi-square test as appropriate.

[b]$p < 0.05$ versus patients with mild acute respiratory distress syndrome (ARDS).

[c]These values were available for 22 patients with mild ARDS both at clinical and 5 cm $H_2O$ positive end-expiratory pressure (PEEP), 25 patients with mild ARDS at clinical PEEP and moderate ARDS at 5 cm $H_2O$ PEEP, and for 59 patients with moderate ARDS both at clinical and 5 cm $H_2O$ PEEP.

[d]$p < 0.05$ versus patients with moderate ARDS.

Data are presented as mean ± SD, median [interquartile range], or $n$ (%), as appropriate. Findings related to total lung tissue and nonaerated lung tissue were assessed by CT scanning performed at 5 cm $H_2O$ PEEP, assumed as standard baseline conditions.

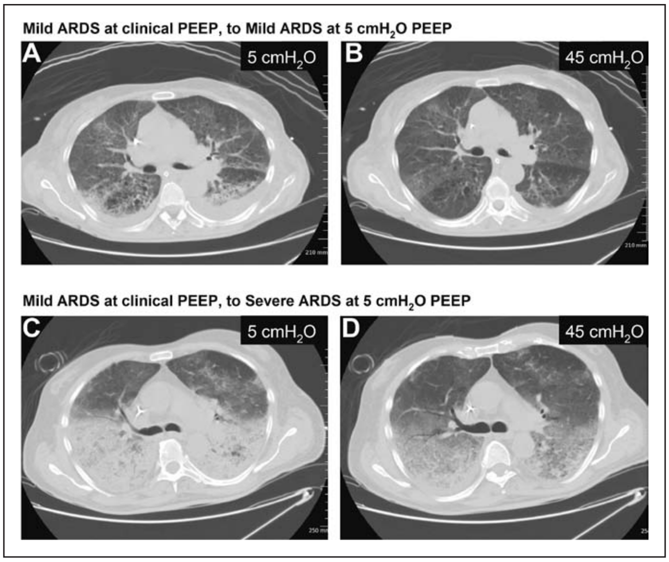


**Figure 2.** Representative CT slices of the lung both at 5 and 45 cm $H_2O$ airway pressure for a patient classified in the mild acute respiratory distress syndrome (ARDS) group both at clinical and 5 cm $H_2O$ positive end-expiratory pressure (PEEP) (**A** and **B**) and for a patient classified in the mild ARDS group at clinical PEEP and in the severe ARDS group at 5 cm $H_2O$ PEEP (**C** and **D**). All CT slices were obtained 2 cm above the diaphragm dome. Lung injury developed in the first patient (A and B) after an episode of severe pneumonia ($Pa{O_2}/F{IO_2}$, 270 mm Hg at the clinical PEEP of 10 cm $H_2O$, 217 mm Hg at 5 cm $H_2O$ PEEP; $Pa{CO_2}$, 49 mm Hg at clinical PEEP, 48 mm Hg at 5 cm $H_2O$ PEEP; respiratory-system elastance, 22.0 cm $H_2O$/L at clinical PEEP, 26.4 cm $H_2O$/L at 5 cm $H_2O$ PEEP). The percentage of potentially recruitable lung was 3%, and the proportion of consolidated lung tissue was 6% of the total lung weight. Lung injury developed in the second patient after an episode of severe pneumonia ($Pa{O_2}/F{IO_2}$, 209 mm Hg at the clinical PEEP of 10 cm $H_2O$, 55 mm Hg at 5 cm $H_2O$ PEEP; $Pa{CO_2}$, 36 mm Hg at clinical PEEP, 44 mm Hg at 5 cm $H_2O$ PEEP; respiratory-system elastance, 27.5 cm $H_2O$/L at clinical PEEP, 18.1 cm $H_2O$/L at 5 cm $H_2O$ PEEP). The percentage of potentially recruitable lung was 38%, and the proportion of consolidated lung tissue was 18% of the total lung weight.

ARDS (**Fig. 4**; and **Table E3 and E4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B141).

### Survival Analysis

ICU mortality significantly increased with ARDS severity, as assessed either at clinical ($p = 0.02$) or at 5 cm $H_2O$ PEEP ($p = 0.002$) (Table 2). When the predictive validity for ICU mortality was evaluated, no differences were observed between the Berlin definition applied at clinical and that applied at either 5 or 15 cm $H_2O$ PEEP (AUROC, 0.626; 95% CI, 0.541–0.711 vs AUROC, 0.622; 95% CI, 0.537–0.707 at 5 cm $H_2O$; $p = 0.92$; and AUROC, 0.587; 95% CI, 0.498–0.676 at 15 cm $H_2O$; $p = 0.37$). When we considered CT-lung injury severity and $Pa{O_2}/F{IO_2}$ as risk factors for mortality, the percentage of potentially recruitable lung was the only variable independently associated with a decreased ICU survival at both univariate and multivariable Cox proportional hazard models after adjustments for clinically variables potentially associated with mortality (**Table 4**). Adjustments also for the severity of lung injury, as denoted by the weight of nonaerated lung tissue, did not modify these results (**Table E5**, Supplemental Digital Content 1, http://links.lww.com/CCM/B141).

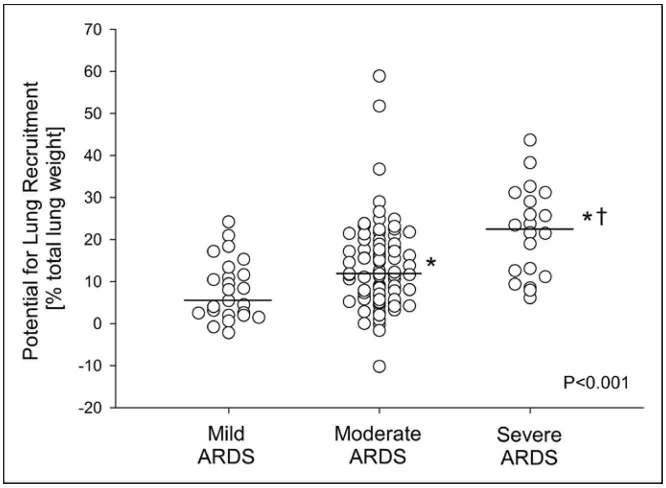


**Figure 3.** Potential for lung recruitment in patients with mild, moderate, and severe acute respiratory distress syndrome (ARDS) classified by applying the Berlin definition at standard 5 cm $H_2O$ positive end-expiratory pressure (PEEP). Data are expressed as dot-density graph, *solid line* representing median values of each group. The potential for lung recruitment denotes the amount of nonaerated lung tissue at 5 cm $H_2O$ PEEP regaining aeration at 45 cm $H_2O$ airway pressure and was expressed as percentage of the total lung tissue weight. The potential for lung recruitment significantly increased moving from each ARDS category, being double in patients with moderate ARDS and three-fold in those with severe ARDS compared with patients with mild ARDS ($p < 0.001$, one-way analysis of variance for all; $^{*}p < 0.05$ versus patients with mild ARDS, $^{\dagger}p < 0.05$ vs patients with moderate ARDS).

## DISCUSSION

Our analysis confirms a valid correlation between ARDS classification according to the recently proposed Berlin definition (2) and the severity of lung injury as assessed by CT scanning, especially in severe ARDS. Nonetheless, we showed that the application of the Berlin definition at standard low PEEP widely reclassifies patients between ARDS categories, depending on their lung recruitability. Furthermore, we observed that only the definition at 5 cm $H_2O$ PEEP provides a clear-cut differentiation between the three categories of ARDS severity in lung recruitability, which appeared an independent risk factor for ICU mortality.

The diagnosis of ARDS is based on respiratory symptoms caused by inflammatory edema, whose extent dictates the severity of the disease. For practical reasons, $Pa{O_2}/F{IO_2}$ ratios are commonly used as surrogates of the extent of pulmonary edema (20). As compared to the previous AECC definition, the Berlin definition, introducing the concepts of moderate and severe ARDS, formalized the association between ARDS severity and the degree of hypoxemia. This approach appears reasonable as moderate and severe ARDS subgroups differ in several physiological variables (2). In our study, lung recruitability significantly increased along ARDS severity, especially in patients with severe ARDS. As the severity of ARDS is crucial in guiding therapy, the Berlin definition, although not free from limitations (25), represents an important step ahead in the field (26).

Despite these findings, we found that the level of clinical PEEP, generally applied to provide an adequate hemoglobin oxygen saturation, may mask the severity of the underlying

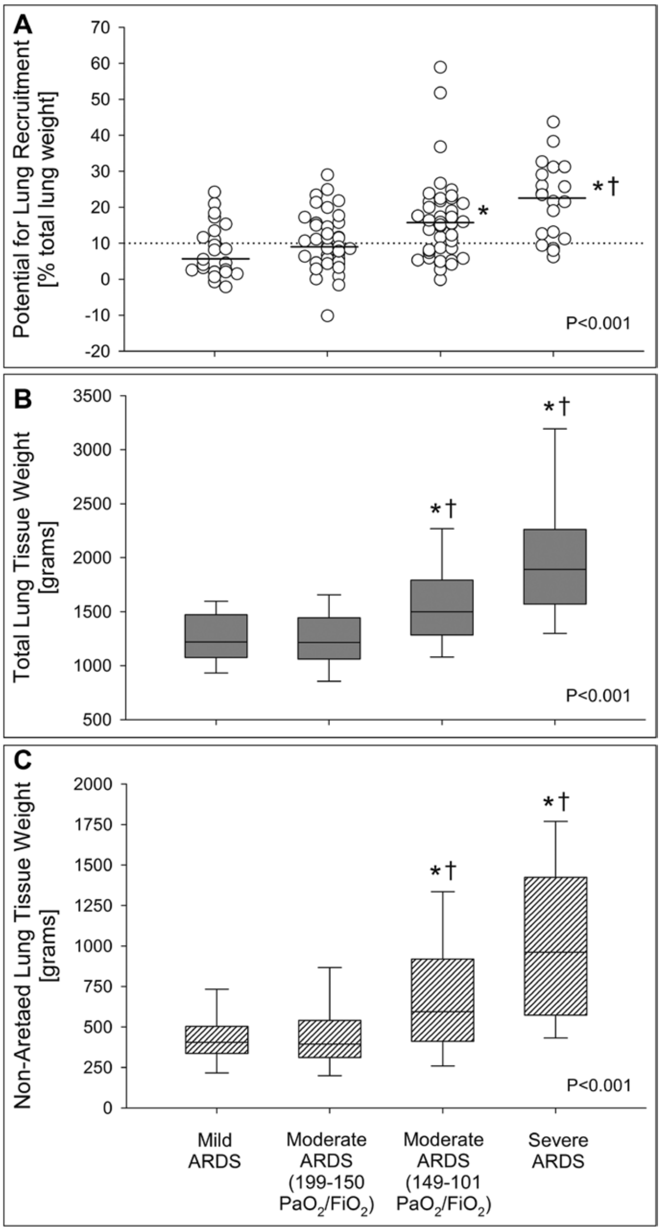


**Figure 4.** Potential for lung recruitment (**A**), total lung tissue (**B**), and nonaerated lung tissue (**C**) detected at 5 cm $H_2O$ positive end-expiratory pressure (PEEP) in patients with mild, moderate-mild, moderate-severe, and severe acute respiratory distress syndrome (ARDS) according to the Berlin definition applied at 5 cm $H_2O$ PEEP. Patients with moderate-mild and moderate-severe ARDS were obtained dividing patients with moderate ARDS according to the $Pa{O_2}/F{IO_2}$ threshold value of 150 mm Hg: patients with moderate-mild ARDS, with a $Pa{O_2}/F{IO_2}$ between 150 and 199 mm Hg, and those with moderate-severe ARDS, with a $Pa{O_2}/F{IO_2}$ between 101 and 149 mm Hg. The potential for lung recruitment is expressed as dot-density graph, *solid lines* representing median values of each group; total lung tissue and nonaerated lung tissue are expressed as median value, interquartile range, and 5° and 95° percentile range. *Dotted line* in A denotes the threshold value of 9% of potentially recruitable lung to define patients with either a higher or a lower potential for lung recruitment. The potential for lung recruitment denotes the amount of nonaerated lung tissue at 5 cm $H_2O$ PEEP regaining aeration at 45 cm $H_2O$ airway pressure and was expressed as percentage of the total lung tissue weight. As shown, no differences were observed between patients with either mild or moderate-mild ARDS, while all the lung morphological characteristics assessed progressively and linearly deteriorated from patients with moderate-mild to those with severe ARDS ($p < 0.001$, one-way analysis of variance for all; $^*p < 0.05$ vs patients with mild ARDS, $^{\dagger}p < 0.05$ vs patients with moderate-mild ARDS).

lung injury, especially in patients with mild ARDS. When PEEP was set at 5 cm $H_2O$, $Pa{O_2}/F{IO_2}$ values sharply decreased in about 50% of the patients, leading to a wide reclassification to moderate and severe ARDS. Several mechanisms have been implied in such discrepancy, including lung recruitability, the applied PEEP, and the distribution of ventilation-to-perfusion matching (19, 27–29). The greater the percentage of the potentially recruitable lung, the greater will be the probability that a given patient, if a higher PEEP is applied, will be classified in a less severe category than the proper category indicated by the underlying injury. Furthermore, the higher the PEEP applied, the greater will be the reduction in cardiac output and venous admixture (28), further masking ARDS severity, whereas a lower PEEP may minimize these effects.

The impact of using a standard ventilatory setting for assessing ARDS severity according to the Berlin definition has been recently proposed in a multicenter prospective study (7). Following previous investigations (5, 6, 30), the authors observed that a $Pa{O_2}/F{IO_2}$ value assessed at PEEP greater than or equal to 10 cm $H_2O$ after 24 hours from ARDS onset was the best indicator of risk stratification, suggesting a lower survival rate in patients in which $Pa{O_2}/F{IO_2}$ derangement persists over time, compared with those in which $Pa{O_2}/F{IO_2}$ ameliorates. Although these findings may have clinical implications (31), no actual standardization of the PEEP level applied was ever evaluated.

We have previously observed that $Pa{O_2}/F{IO_2}$ at 5 cm $H_2O$ PEEP is a relatively accurate predictor of a higher versus a lower lung recruitability (10). In this study, we observed that when the Berlin definition is applied at 5 cm $H_2O$ PEEP, a more accurate and parallel relationship may be obtained between severity and lung recruitability. Of note, the potentially recruitable lung was the only CT-derived variable independently associated with ICU mortality, even after adjustments for clinically relevant variables and the severity of lung injury, that is, the amount of nonaerated lung tissue. It is conceivable that the Berlin ARDS classification at 5 cm $H_2O$ PEEP may allow a bedside estimate of lung recruitability (32), therefore better predicting the potential response to specific therapeutical procedures, such as higher PEEP or prone positioning (17, 33).

Even when considering ARDS classification at 5 cm $H_2O$ PEEP, lung recruitability varied widely among patients with moderate ARDS. However, when this category was further divided according to a $Pa{O_2}/F{IO_2}$ of 150 mm Hg, no differences were observed between patients with mild and those with moderate-mild ARDS. By contrast, when moving from patients with moderate-mild to severe ARDS, both lung recruitability and edema progressively and linearly deteriorated. These findings suggest that a $Pa{O_2}/F{IO_2}$ equal to 150 mm Hg, when assessed at standard 5 cm $H_2O$ PEEP, is a crucial threshold below which lung recruitability and the severity of lung injury progressively increase.

Predictive validity for mortality of the Berlin definition was shown to be significantly superior to that of the previous AECC definition although in both cases AUROC values indicated poor accuracy (ranging between 0.55 and 0.60) (2). Similar findings were observed in a large prospective study in which neither the severity stratification proposed with the Berlin

**TABLE 4. Univariate and Multivariable Cox Models for ICU Mortality**

| Characteristics | Univariate | | Multivariable | |
|---|---|---|---|---|
| | HR | $p^a$ | HR | $p^a$ |
| Total lung tissue, g | 1.00 (1.00–1.00) | 0.66 | 1.00 (1.00–1.00) | 0.47 |
| Nonaerated lung tissue, g | 1.00 (1.00–1.00) | 0.24 | 1.00 (1.00–1.00) | 0.73 |
| Nonaerated lung tissue, % | 1.01 (0.99–1.03) | 0.29 | 1.01 (0.99–1.03) | 0.32 |
| Poorly aerated lung tissue, % | 1.01 (0.99–1.03) | 0.56 | 1.01 (0.98–1.03) | 0.68 |
| Normally aerated lung tissue, % | 0.98 (0.96–1.00) | 0.007 | 0.98 (0.95–1.01) | 0.10 |
| Hyperinflated lung tissue, % | 1.14 (0.90–1.47) | 0.27 | 1.13 (0.85–1.51) | 0.39 |
| Consolidated lung tissue, % | 0.99 (0.96–1.01) | 0.23 | 0.99 (0.96–1.01) | 0.36 |
| Potentially recruitable lung, % | 1.04 (1.02–1.06) | 0.002 | 1.04 (1.01–1.07) | 0.007 |
| $Pa_{O_2}/F_{IO_2}$ at clinical PEEP, mm Hg | 1.00 (0.99–1.00) | 0.05 | 1.00 (0.99–1.00) | 0.62 |
| $Pa_{O_2}/F_{IO_2}$ at 5 cm $H_2O$ PEEP, mm Hg | 0.99 (0.99–1.00) | 0.07 | 1.00 (0.99–1.00) | 0.38 |
| $Pa_{O_2}/F_{IO_2}$ at 15 cm $H_2O$ PEEP, mm Hg | 1.00 (0.99–1.00) | 0.03 | 1.00 (0.99–1.00) | 0.16 |

HR = hazard ratio, PEEP = positive end-expiratory pressure.

[a]*p* values refer to Cox model analysis performed either as univariate or multivariable analysis.

Data are presented as hazard ratio and 95% CI with increment of one unit for one point gram, percentage, or mm Hg, as appropriate. The following covariates, deemed a priori as clinically relevant, were considered in the multivariable models: Simplified Acute Physiology Score II score, age, normalized minute ventilation, and days of mechanical ventilation before the study. Data on survival time were available for 119 patients.

definition nor $Pa_{O_2}/F_{IO_2}$ values were associated with mortality (25). In our cohort, the predictive validity for mortality of the Berlin definition showed a similar low accuracy, independently of the applied PEEP level. Nonetheless, lung recruitability appeared an independent risk factor for ICU mortality. These findings indicate that the assessment of the Berlin definition at low PEEP, although not providing per se a solid accuracy for survival prediction, may help in estimating the degree of lung recruitability, which may appear an important feature for setting mechanical ventilation and for risk stratification.

Our study has certain limitations. First, it is based on a retrospective analysis, in which an accurate control for potential confounding factors was not feasible. Nonetheless, we think that the similarity of the study protocols applied in each trial has limited heterogeneity of data collection. Second, the time elapsed from ARDS diagnosis to CT scanning was not standardized. Although we cannot exclude an effect on CT-lung injury severity, in our previous investigation, lung recruitability was not influenced by the duration of ventilation before CT scanning (10). Third, we observed a lower prevalence of severe ARDS compared with previous investigations (2, 7, 25). Although we cannot exclude a selection bias due to the retrospective nature of our study, we think this finding may be related to the high lung recruitability of patients with severe ARDS and the consequent effect of the recruitment maneuver applied before data recording even at clinical PEEP.

## CONCLUSIONS

This report confirms that the risk stratification proposed by the novel ARDS Berlin definition based on $Pa_{O_2}/F_{IO_2}$ is a reasonable tool to describe the severity of lung injury. Nonetheless, it also shows that the clinical PEEP applied when assessing $Pa_{O_2}/F_{IO_2}$ may mask the underlying ARDS severity and that the application of the definition at 5 cm $H_2O$ PEEP more accurately matches ARDS lung injury severity and recruitability, providing important information to guide ventilator strategies and to assess mortality risk.

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