ORIGINAL ARTICLE

Positive End-Expiratory Pressure Lower Than the ARDS Network Protocol Is Associated with Higher Pediatric Acute Respiratory Distress Syndrome Mortality

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Abstract

Rationale: The ARDS Network (ARDSNet) used a positive end-expiratory pressure (PEEP)/$F_{I_{O_2}}$ model in many studies. In general, pediatric intensivists use less PEEP and higher $F_{I_{O_2}}$ than this model.

Objectives: To evaluate whether children managed with PEEP lower than recommended by the ARDSNet PEEP/$F_{I_{O_2}}$ model had higher mortality.

Methods: This was a multicenter, retrospective analysis of patients with pediatric acute respiratory distress syndrome (PARDS) managed without a formal PEEP/$F_{I_{O_2}}$ protocol. Four distinct datasets were combined for analysis. We extracted time-matched PEEP/$F_{I_{O_2}}$ values, calculating the difference between PEEP level and the ARDSNet-recommended PEEP level for a given $F_{I_{O_2}}$. We analyzed the median difference over the first 24 hours of PARDS diagnosis against ICU mortality and adjusted for confounding variables, effect modifiers, or factors that may have affected the propensity to use lower PEEP.

Measurements and Main Results: Of the 1,134 patients with PARDS, 26.6% were managed with lower PEEP relative to the amount of $F_{I_{O_2}}$ recommended by the ARDSNet protocol. Patients managed with lower PEEP experienced higher mortality than those who were managed with PEEP levels in line with or higher than recommended by the protocol ($P < 0.001$). After adjustment for hypoxemia, inotropes, comorbidities, severity of illness, ventilator settings, nitric oxide, and dataset, PEEP lower than recommended by the protocol remained independently associated with higher mortality (odds ratio, 2.05; 95% confidence interval, 1.32–3.17). Findings were similar after propensity-based covariate adjustment (odds ratio, 2.00; 95% confidence interval, 1.24–3.22).

Conclusions: Patients with PARDS managed with lower PEEP relative to $F_{I_{O_2}}$ than recommended by the ARDSNet model had higher mortality. Clinical trials targeting PEEP management in PARDS are needed.

Keywords: acute respiratory distress syndrome; acute lung injury; positive end expiratory pressure; ARDS Network; pediatrics

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At a Glance Commentary

Scientific Knowledge on the Subject: Optimal methods to titrate positive end-expiratory pressure (PEEP) remain an active area of controversy in the management of patients with acute respiratory distress syndrome (ARDS). Although a PEEP/$F_{I_{O_2}}$ protocol inspired by the ARDS Network has been used in a variety of clinical trials, many intensive care practitioners use less PEEP and higher $F_{I_{O_2}}$ than this protocol, particularly in pediatric ARDS.

What This Study Adds to the Field: Through secondary analysis of four previously published datasets containing more than 1,000 patients with pediatric ARDS managed without a formal PEEP/$F_{I_{O_2}}$ protocol, we found that patients managed with lower PEEP than would be recommended by the PEEP/$F_{I_{O_2}}$ protocol for a given $F_{I_{O_2}}$ experienced higher mortality than those who were managed either per protocol or with higher relative PEEP. These findings held in stratified analyses and after adjustment for confounding variables, effect modifiers, and propensity-based covariate adjustment. Clinical trials are needed.

Although adequate positive end-expiratory pressure (PEEP) is essential to prevent atelectrauma in patients with acute respiratory distress syndrome (ARDS), observational data in both adults and children highlight that many patients with ARDS are on PEEP lower than recommended (1–3). Although PEEP titration methods are controversial, previous ARDS studies have used a PEEP/$F_{I_{O_2}}$ titration table popularized by the ARDS Network (ARDSNet) (3–5). This table recommends combinations of PEEP and $F_{I_{O_2}}$, such that both are escalated or deescalated in tandem as hypoxemia worsens or improves. Although other approaches may have advantages, degree of hypoxemia is an important consideration in PEEP management (4, 6, 7).

There is substantial variability in PEEP/$F_{I_{O_2}}$ combinations chosen during usual care ventilation, with a proclivity toward increasing $F_{I_{O_2}}$ over PEEP for hypoxemia (2, 8–11). Hence, although PEEP/$F_{I_{O_2}}$ tables are standard in clinical trials, clinical practice appears quite discrepant. This may be because there are limited data directly evaluating whether patients managed congruent with these PEEP/$F_{I_{O_2}}$ combinations have better outcomes than those managed with different combinations.

This issue becomes even more important in pediatrics, as there are virtually no studies examining the relationship between PEEP and mortality in ARDS, although several confirm the PEEP/$F_{I_{O_2}}$ table recommendations from ARDSNet are rarely followed in children (8, 9, 11–14). In general, there is reluctance to escalate PEEP above 10 cm H_2O, particularly for younger children (8, 11). Through secondary analysis of aggregated data from four previously published studies of children with pediatric ARDS (PARDS) (11, 15–18), we sought to determine if patients managed with PEEP levels lower than recommended by the ARDSNet table for a given $F_{I_{O_2}}$ in actual practice had higher mortality than patients who were managed with PEEP levels consistent with or higher than recommended by the ARDSNet table.

Methods

We combined four previously published datasets of invasively mechanically ventilated children with PARDS (15–18). Two of the datasets were gathered retrospectively by reviewing the electronic health records of pediatric ICU (PICU) patients admitted to Children's Hospital Los Angeles (CHLA) from 2000 to 2007 (15) and 2009 to 2013 (16). One dataset was gathered prospectively from patients admitted to the Children's Hospital of Philadelphia (CHOP) from 2011 to 2016 (17, 18). The fourth dataset was gathered prospectively across eight hospitals in the Collaborative Pediatric Critical Care Research Network (CPCCRN) from 2011 to 2012 (11). We excluded CHOP and CHLA patients from the CPCCRN dataset to prevent any potential patient overlap. The parent studies were approved by their respective institutional review boards, and anonymous data were aggregated for this study.

PARDS Eligibility

Although inclusion criteria for each of the four studies differed slightly, we included patients who met the Pediatric Acute Lung Injury Consensus Conference definition of PARDS while on invasive mechanical ventilation (1). Hypoxemia for the PARDS definition was based on oxygenation index (OI) greater than or equal to 4 or oxygen saturation index greater than or equal to 5. The CHLA dataset from 2000 to 2007 and the CHOP dataset included patients only on the basis of OI, whereas the CHLA dataset from 2009 to 2013 and the CPCCRN dataset included patients using oxygen saturation index when OI was not available. All patients had a PARDS trigger (i.e., pneumonia, sepsis), with pulmonary parenchymal disease on chest radiograph. Patients whose respiratory failure was believed to be primarily due to cardiac disease were excluded. Although required to meet Pediatric Acute Lung Injury Consensus Conference criteria for inclusion, because our question of interest focused on PEEP (which affects mean airway pressure in the OI calculation), we chose to group hypoxemia severity on the basis of the Berlin definition ($Pa_{O_2}/F_{I_{O_2}}$ [PF] ratio), imputing PF ratio from the ratio of oxygen saturation as measured by pulse oximetry to $F_{I_{O_2}}$ using previously published equations (19) when an arterial blood gas measurement was not available.

PEEP/$F_{I_{O_2}}$ Scoring

We extracted time-matched PEEP and $F_{I_{O_2}}$ values every 6 hours over the first 24 hours after diagnosis. $F_{I_{O_2}}$ measurements were categorized into intervals of 0.05, ranging from 0.21 to 1.0. For each $F_{I_{O_2}}$/PEEP pair, we calculated how far the set PEEP for a given $F_{I_{O_2}}$ was from the "low PEEP" ARDSNet protocol–recommended PEEP. For example, for a patient on 0.6 $F_{I_{O_2}}$, the ARDSNet PEEP/$F_{I_{O_2}}$ table recommends a PEEP of 10 cm H_2O. If the patient was actually on a PEEP of 5 cm H_2O, a PEEP discordance score of -5 would be assigned. For $F_{I_{O_2}}$ values in which multiple PEEP levels are permitted by ARDSNet, we used the level closest to the clinical PEEP (i.e., clinical PEEP = 6 cm H_2O, ARDSNet PEEP allowed 8–10 cm H_2O, PEEP discordance score = $6 - 8 = -2$ cm H_2O). We subsequently took the median score over the first 24 hours of PARDS diagnosis (using the initial time point plus four 6-hr

Table 1. Characteristics and Outcomes of Study Cohort, Stratified by Pediatric ICU Mortality

Variable	Overall (*N = 1,134*)	Survivors (*n = 923*)	Nonsurvivors (*n = 211*)	*P* Value
Demographics				
Age, mo	46.6 (13.2–137.6)	44.4 (12.6–128.4)	75 (16.2–164.6)	0.01
Sex, male	621 (54.8)	503 (54.5)	118 (55.9)	0.70
Race (*n* = 1,065)				0.16
White	305 (28.6)	245 (28.4)	60 (29.7)	
Hispanic	332 (31.2)	267 (30.9)	65 (32.2)	
Black	199 (18.7)	172 (19.9)	27 (13.4)	
Other race	229 (21.5)	179 (20.7)	50 (24.8)	
ARDS trigger (*n* = 1,065)				
Pneumonia	660 (58.2)	549 (59.4)	111 (52.6)	0.07
Sepsis	323 (28.5)	242 (26.2)	81 (38.4)	<0.001
Drowning	20 (1.9)	16 (1.9)	4 (2.0)	0.9
Aspiration	82 (7.7)	65 (7.5)	17 (8.4)	0.67
Trauma	72 (6.8)	53 (6.1)	19 (9.4)	0.09
Dataset				0.005
CHLA 2000–2007	358 (31.6)	281 (78.5)	77 (21.5)	
CHLA 2009–2013	254 (22.4)	194 (76.4)	60 (23.6)	
CHOP	453 (40.0)	388 (85.6)	65 (14.4)	
CPCCRN	69 (6.1)	60 (87.0)	9 (13.0)	
Comorbidities (*n* = 1,065)				
Immunodeficiency	248 (23.3)	162 (18.7)	86 (42.6)	<0.001
Cancer	161 (15.1)	107 (12.4)	54 (26.7)	<0.001
Stem cell transplant	64 (6.0)	27 (3.1)	37 (18.3)	<0.001
Solid organ transplant	41 (3.8)	38 (4.4)	3 (1.5)	0.05
Neurologic disease	260 (24.4)	219 (25.4)	41 (20.3)	0.13
Data at PARDS diagnosis				
ARDS severity				<0.001
PF > 300	44 (3.9)	37 (4)	7 (3.3)	
PF 200–300	264 (23.3)	229 (24.8)	35 (16.6)	
PF 100–200	500 (44.1)	427 (46.2)	73 (34.6)	
PF ⩽ 100	326 (28.8)	230 (24.9)	96 (45.5)	
PRISM III raw score	11 (6–17)	9 (5–15)	17 (11–27)	<0.001
PF ratio	147 (91–207)	153 (101–212)	114 (65–180)	<0.001
OI	10.0 (6.3–17.7)	9.3 (6.0–15.6)	15.2 (7.4–25.8)	<0.001
F_{IO_2}	0.60 (0.44–0.90)	0.55 (0.40–0.80)	0.78 (0.50–1.00)	<0.001
PEEP, cm H_2O	8.0 (6.0–10.0)	8.0 (6.0–10.0)	8.5 (6.0–10.0)	0.03
Data over first 24 h (*n* = 1,005)				
ARDS severity				<0.001
PF > 300	115 (10.8)	189 (10.3)	26 (13.2)	
PF 200–300	408 (38.5)	362 (41.9)	46 (23.4)	
PF 100–200	420 (39.6)	345 (39.9)	75 (38.1)	
PF ⩽ 100	118 (11.2)	68 (7.9)	50 (25.4)	
Pa_{O_2}, mm Hg (*n* = 938)	89 (76–108)	89 (77–106)	91 (71–114)	0.94
Day 1 average Pa_{O_2} range	*n* = 938	*n* = 750	*n* = 188	<0.001
Pa_{O_2} ⩽ 60 mm Hg	53 (5.7)	30 (4)	23 (12.2)	
Pa_{O_2} 60–80 mm Hg	253 (27)	207 (27.6)	46 (24.5)	
Pa_{O_2} 80–100 mm Hg	314 (33.5)	269 (35.9)	45 (23.9)	
Pa_{O_2} > 100 mm Hg	318 (33.9)	244 (32.5)	74 (39.4)	
PF ratio	198 (141–253)	205 (148–253)	170 (99–242)	<0.001
OI	7.6 (5.3–13.0)	7.2 (5.2–11.4)	11.2 (6.2–22.8)	<0.001
F_{IO_2}	0.50 (0.40–0.60)	0.46 (0.40–0.57)	0.60 (0.46–0.80)	<0.001
PEEP, cm H_2O	8.8 (6.7–10.8)	8.4 (6.6–10.3)	10.0 (7.5–12.0)	<0.001
V_T, ml/kg	7.5 (6.5–8.6)	7.5 (6.5–8.6)	7.4 (6.1–8.5)	0.31
PIP, cm H_2O	28 (24.5–33)	28 (24–32)	31 (26.7–36)	<0.001
Driving pressure, cm H_2O	19.5 (16–23)	19 (16–22.6)	20.5 (18–24.5)	<0.001
Inotropes	630 (59.2)	474 (54.9)	156 (77.2)	<0.001
Nitric oxide	223 (21)	159 (18.4)	64 (31.6)	<0.001

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CHLA = Children's Hospital Los Angeles; CHOP = Children's Hospital of Philadelphia; CPCCRN = Collaborative Pediatric Critical Care Research Network; OI = oxygenation index; OSI = oxygen saturation index; PARDS = pediatric acute respiratory distress syndrome; PEEP = positive end-expiratory pressure; PF = Pa_{O_2}/F_{IO_2}; PIP = peak inspiratory pressure; PRISM = Pediatric Risk of Mortality.

Data are presented as median (interquartile range) or *n* (%). When a Pa_{O_2} metric was not available, PF was calculated from the ratio of oxygen saturation measured by pulse oximetry to F_{IO_2}, and OI was calculated from OSI using previously published formulae (19). Race, ARDS triggers, and comorbidities were not available in the CPCCRN data, so the total number is reduced to 1,065. Some patients did not have available data 24 hours after PARDS diagnosis (died, extubated, or no PF ratio, OI, or OSI available), so the number is reduced to 1,005. Driving pressure was calculated as PIP minus PEEP, as most patients were on pressure-regulated modes of ventilation, and inspiratory holds were not routinely performed. The percentages refer to the percentage of overall patients, survivors, or nonsurvivors with a given variable. *P* values compare the difference between survivors and nonsurvivors, among variables, or among groupings of variables (i.e., $P < 0.001$ for PARDS severity implies difference in PARDS severity categories between survivors and nonsurvivors, without *post hoc* comparison of which groups are different).

blocks [when available]) for analysis. A composite variable deemed "low PEEP" was categorized for patients with PEEP below protocol for a given $F_{I_{O_2}}$ and was used for multivariable analysis. None of the hospitals had a formal protocol for PEEP/$F_{I_{O_2}}$ management, although CHOP used a strategy in which an inability to wean $F_{I_{O_2}}$ below 0.60 after intubation warranted escalation of PEEP to 8 to 10 cm H_2O.

Additional Variables

From each dataset (when available), we extracted demographic data, diagnoses, ventilator settings, use of nitric oxide, comorbidities, use of inotrope/vasopressor medications within 24 hours of PARDS diagnosis, and outcomes. These additional variables were homogenized among datasets to ensure similar case definitions through discussion among the principal investigators of each study and on the basis of case report forms. Many of these supplementary data were not available from the CPCCRN dataset, so these patients were excluded from multivariable analyses. PICU mortality was the primary outcome.

Outcome Measures and Analysis

The primary objective was to evaluate whether patients managed with lower PEEP for a given $F_{I_{O_2}}$ than recommended by the ARDSNet table in actual practice had higher mortality than patients managed with PEEP in line with or higher than what would be recommended from ARDSNet. We considered this combination variable because on a univariate basis, higher PEEP and higher $F_{I_{O_2}}$ are associated with mortality (they are both increased in the setting of hypoxemia). This combination variable allowed us to examine the potential impact of ventilator strategies that prioritize one value over the other to achieve an oxygenation target, because these variables are changed to a different extent by providers in similar patient states. Secondary objectives were to determine whether this relationship was consistent among all datasets and whether it was modified by variables that may affect PEEP choice, such as hypoxemia (i.e., PF ratio), demographics and diagnoses, nitric oxide, or other factors.

We report PICU mortality as a function of PEEP discordance relative to the ARDSNet table. We next explored factors that may be associated with PICU mortality or PEEP lower than recommended by the protocol for a given $F_{I_{O_2}}$. Continuous variables were analyzed against mortality with a Mann-Whitney *U* test, as data were often not normally distributed. Categorical data were analyzed with a chi-square test with Yates correction. ICU mortality was also examined as a function of PEEP lower than the protocol, with survival analysis, stratified by initial PF ratio. We then constructed a multivariate logistic regression model retaining variables that were either associated with PICU mortality or resulted in a greater than 15% change in the parameter estimates for PEEP lower than the protocol, also considering multiplicative interaction terms (retaining those with $P < 0.1$). Given the high correlation among many ventilator and hypoxemia variables, for multivariable models we used PF ratio (imputed from oxygen saturation as measured by pulse oximetry to $F_{I_{O_2}}$ ratio when Pa_{O_2} not available) instead of OI because of the overlap of mean airway pressure with PEEP and other ventilator

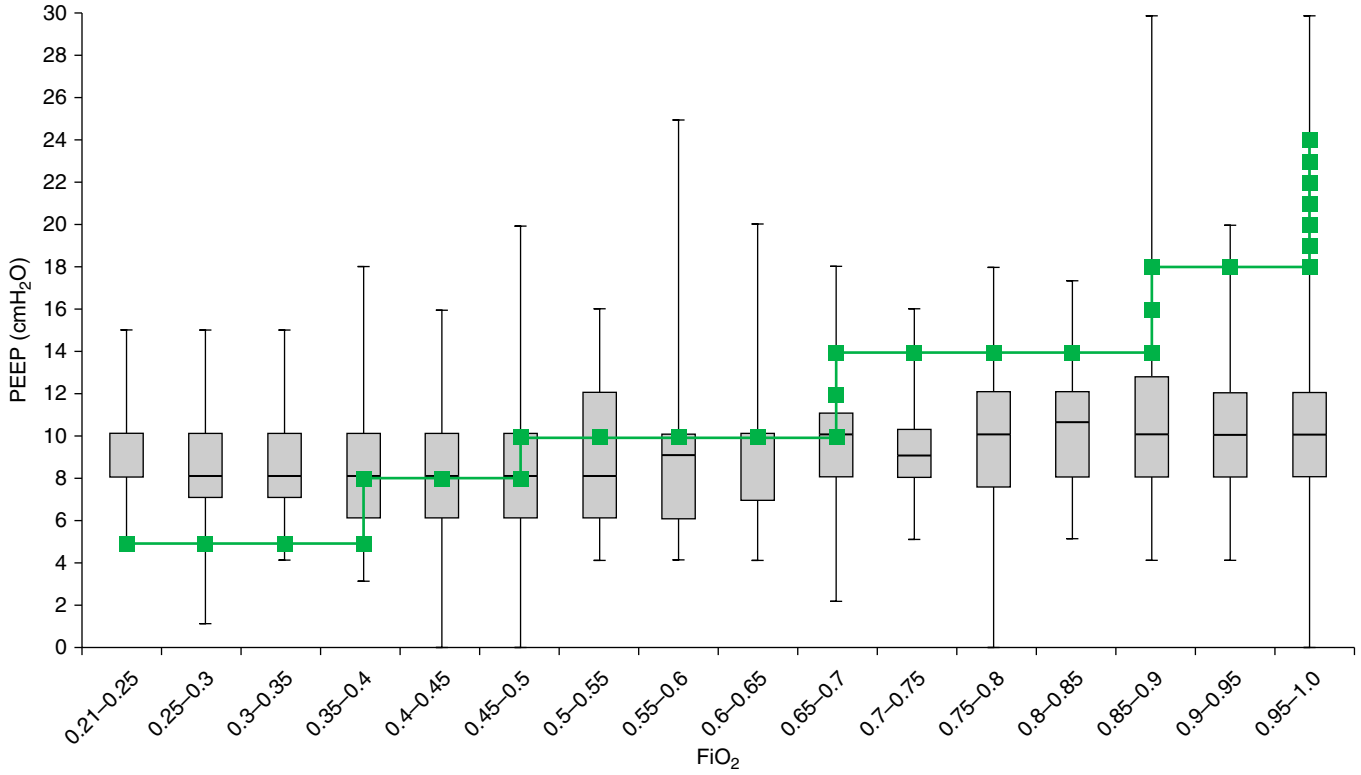

Figure 1. All pediatric acute respiratory distress syndrome (PARDS) positive end-expiratory pressure (PEEP)/$F_{I_{O_2}}$ combinations. Actual PEEP values as a function of actual $F_{I_{O_2}}$ levels (median [bar] and interquartile range [box]) for all patients with PARDS for the first day of mechanical ventilation after PARDS diagnosis. The superimposed line represents the ARDS Network protocol target combinations of PEEP/$F_{I_{O_2}}$. In general, clinicians used more PEEP than recommended when $F_{I_{O_2}}$ was less than 0.4 and used less PEEP than recommended when $F_{I_{O_2}}$ was more than 0.5. Median PEEP level did not exceed 10 cm H_2O, regardless of $F_{I_{O_2}}$.

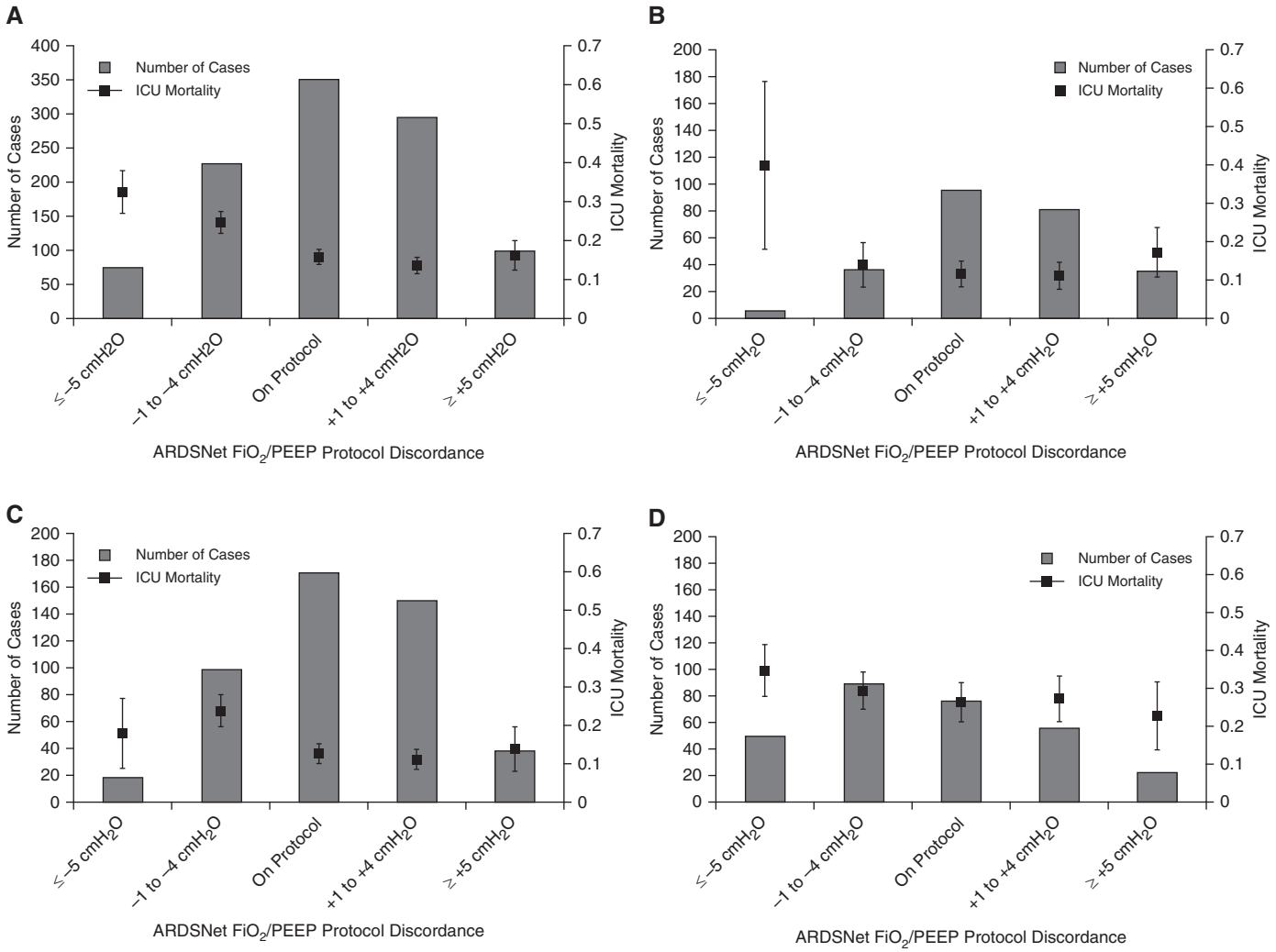

Figure 2. Unadjusted pediatric acute respiratory distress syndrome (PARDS) mortality as a function of positive end-expiratory pressure (PEEP) discordance from the ARDS Network (ARDSNet) PEEP/$F_{I_{O_2}}$ protocol for all patients, and stratified by initial $Pa_{O_2}/F_{I_{O_2}}$ (PF) ratio group. Total $N = 1{,}134$ with 18.6% mortality. Total number of patients with PARDS in each PEEP range is represented by the bars, and ICU mortality (with SE) is represented by the squares. (*A*) All patients with PARDS. There was approximately an even split between patients managed with PEEP below protocol, per protocol, and above protocol. PEEP lower than recommended by the ARDSNet protocol for a given $F_{I_{O_2}}$ was associated with higher mortality. The lowest mortality occurred when PEEP was 1 to 4 cm H_2O above protocol. (*B*) PF 200 to 300; (*C*) PF 100 to 200; (*D*) PF less than or equal to 100. The general trend that mortality is higher for those with PEEP lower than protocol is consistent across all initial PF subgroups. As initial PF ratio worsens, the number of patients managed with PEEP lower than protocol increases.

settings. We selected other variables, which were highly correlated with one another on the basis of a correlation matrix (i.e., driving pressure and peak inspiratory pressure), retaining the variable with the highest univariate association with the outcome, to avoid issues of colinearity. Finally, a propensity score was created to model clinical and severity-of-illness factors associated with PEEP lower than the protocol, considering all variables with a univariate relationship ($P < 0.2$), retaining variables that maintained independent relationships with low PEEP ($P < 0.1$). This propensity score was used as covariate adjustment when further analyzing the independent relationship between PEEP lower than the protocol and PICU mortality. Analysis was performed using Microsoft Excel (Microsoft Corporation), Statistica version 12 (StatSoft), and Stata version 10 (StataCorp).

Sensitivity Analysis

We performed a sensitivity analysis stratifying by those with persistent hypoxemia (PF ⩽ 200) at 24 hours. In addition, because of notable differences between CHOP and CHLA datasets, we performed subgroup analyses within datasets and did comparative analyses between datasets. For the CHLA patients only, we examined whether the relationship was similar on Day 2 and 3 of mechanical ventilation. Additional subgroup analyses can be found in the online supplement.

Results

Description of Cohort

From the four datasets, 1,134 patients were included (358 CHLA 2000–2007, 254

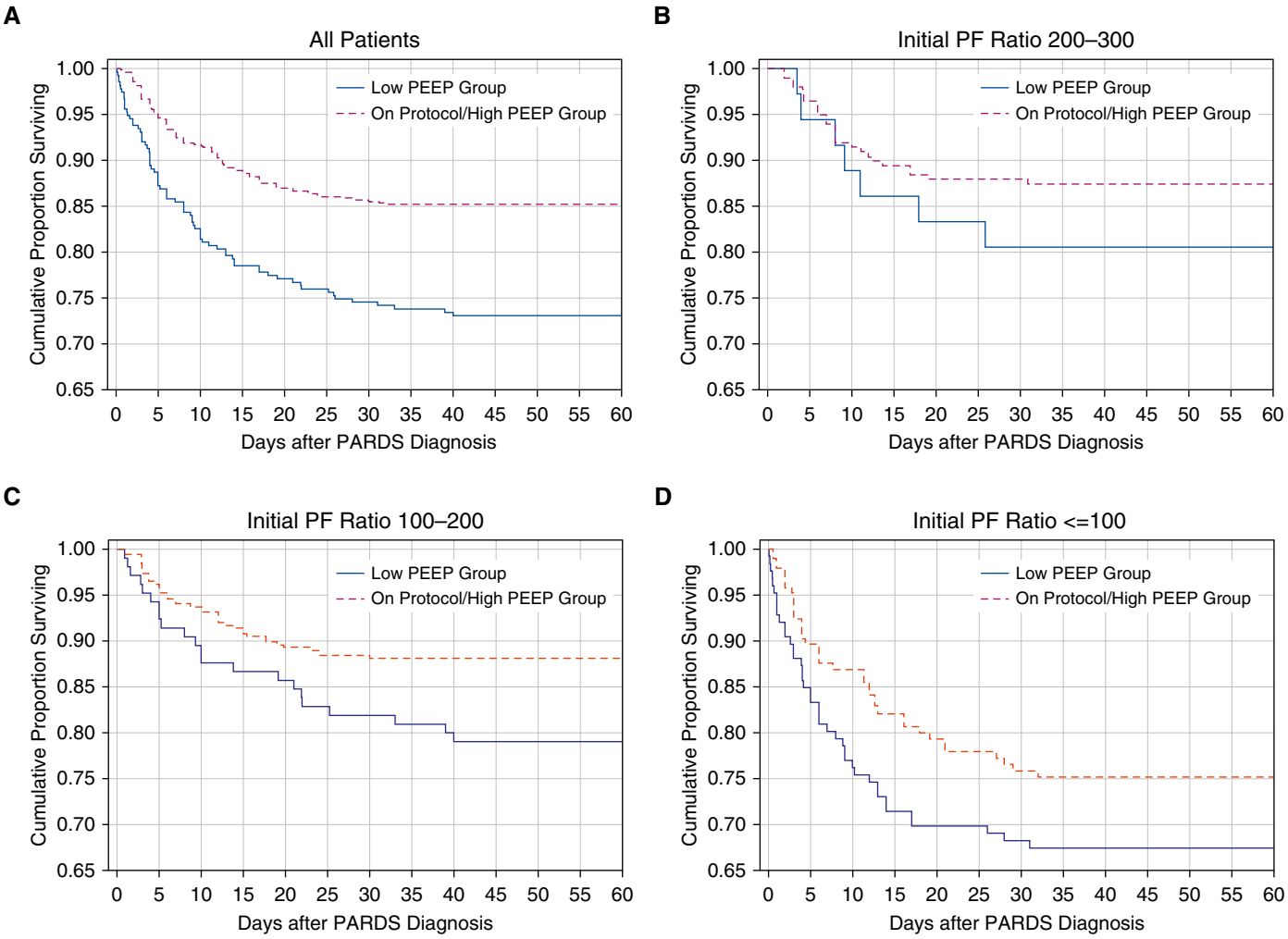

Figure 3. Survival curves for patients on positive end-expiratory pressure (PEEP) lower than recommended by the protocol versus PEEP in line or higher than recommended by the protocol for a given F_{IO_2}, stratified by initial Pa_{O_2}/F_{IO_2} (PF) ratio. (*A*) All patients; (*B*) PF 200 to 300; (C) PF 100 to 200; (*D*) PF less than or equal to 100. For all patients, use of PEEP lower than recommended by the protocol for a given F_{IO_2} was associated with higher mortality ($P < 0.0001$). When subgrouping by initial PF ratio, the trends were consistent, but only statistically significant for PF between 100 and 200 (PF < 100, $P = 0.3$; PF 100–200, $P = 0.004$; PF 200–300, $P = 0.4$). PARDS = pediatric acute respiratory distress syndrome.

CHLA 2009–2013, 453 CHOP, and 69 CPCCRN). Overall mortality was 18.6%. Using Berlin classifications, 44 had PF greater than 300 (3.9%; 15.9% mortality), 264 had PF 200 to 300 (23.3%; 13.3% mortality), 500 had PF 100 to 200 (44.1%; 14.6% mortality), and 326 had PF less than or equal to 100 (28.8%; 29.5% mortality). Patient characteristics of the aggregate cohort stratified by mortality are summarized in Table 1. The mode of conventional ventilation was pressure control in 63% of patients (>97% of CHLA patients), and pressure-regulated volume control in 36.7% of patients (93% of CHOP patients).

There was variability in PEEP/F_{IO_2} combinations chosen in actual practice (Figure 1). In general, F_{IO_2} was prioritized over PEEP as hypoxemia worsened. Overall, 302 (26.6%) patients were managed with PEEP lower than ARDSNet protocol recommendations, 351 (31.0%) were managed per protocol, 394 (34.7%) were managed with PEEP higher than protocol, and 87 (7.7%) did not have adequate PEEP data for Day 1 of ARDS (5.7% of CHOP, 14.5% of CHLA 2000–2007, 3.1% of CHLA 2009–2013, 1.4% CPCCRN).

PEEP Discordance

On unadjusted analysis, there was a dose-dependent trend that patients managed with PEEP less than recommended by the protocol for a given F_{IO_2} for the first 24 hours of PARDS diagnosis had higher mortality, with the highest survival appearing to be with PEEP levels 1 to 4 cm H_2O above what would be recommended by the protocol (Figure 2A). When stratifying by initial PF ratio, this pattern was consistent, with the largest effect seen in those with PF ratio between 100 and 200 (Figures 2B–2D). Overall, patients managed with PEEP lower than recommended by the protocol experienced higher mortality (26.5% vs. 14.9%, $P < 0.001$). Although this trend was consistent among all initial PF ratio groups, it was only statistically significant in those with PF ratio between 100 and 200 (PF < 100, 31% vs. 26%, $P = 0.3$; PF 100–200, 22.6% vs. 11.8%, $P = 0.004$; PF 200–300, 17.1% vs. 12.3%, $P = 0.4$; Figures 3A–3D).

Because higher F_{IO_2} relative to PEEP may be a reflection of disease severity or

Table 2. Variables Associated with the Propensity to Use Lower Positive End-Expiratory Pressure Relative to the ARDS Network Model

Variable	Overall (*N* = *1,047*)	High PEEP/On-Protocol PEEP (*n* = *745*)	Low PEEP (*n* = *302*)	*P* Value
Demographics				
Age, mo	46.8 (13.2–141.0)	49.2 (13.2–132.4)	42.0 (11.9–154.0)	0.99
Sex, male	574 (54.8)	404 (54.2)	170 (56.3)	0.54
Race (*n* = 979)				0.002
White	284 (29.0)	223 (31.7)	61 (22.2)	
Hispanic	299 (30.5)	193 (27.4)	106 (38.6)	
Black	182 (18.6)	135 (19.2)	47 (17.1)	
Other race	214 (21.9)	153 (21.7)	61 (22.2)	
ARDS trigger (*n* = 979)				
Pneumonia	611 (58.4)	443 (59.5)	168 (55.6)	0.25
Sepsis	303 (28.9)	202 (27.1)	101(33.4)	0.04
Drowning	19 (1.9)	14 (2.0)	5 (1.8)	0.86
Aspiration	70 (7.1)	55 (7.8)	15 (5.4)	0.20
Trauma	62 (6.4)	43 (6.1)	20 (7.3)	0.5
Dataset				<0.001
CHLA 2000–2007	306 (29.3)	162 (52.9)	144 (47.1)	
CHLA 2009–2013	246 (23.5)	168 (68.3)	78 (31.7)	
CHOP	427 (40.8)	374 (87.6)	53 (12.4)	
CPCCRN	68 (6.5)	41 (60.3)	27 (39.7)	
Comorbidities (*n* = 979)				
Immunodeficiency	230 (23.5)	170 (24.1)	60 (21.9)	0.44
Cancer	150 (15.3)	115 (16.3)	35 (12.7)	0.15
Stem cell transplant	57 (5.8)	45 (6.4)	12 (4.3)	0.22
Solid organ transplant	40 (4.1)	31 (4.4)	9 (3.3)	0.42
Neurologic disease	237 (24.2)	164 (23.3)	73 (26.6)	0.29
Data at PARDS diagnosis				
PARDS severity				<0.001
PF > 300	32 (2)	24 (3.2)	8 (2.7)	
PF 200–300	252 (24.1)	211 (28.3)	41 (13.6)	
PF 100–200	472 (45.1)	357 (47.9)	115 (38.15)	
P ⩽ 100	291 (27.8)	153 (20.5)	138 (45.7)	
PRISM III raw score	11 (6–17)	11 (5–17)	11 (6–19)	0.05
PF ratio	147 (91–207)	156 (109–217)	109 (66–162)	<0.001
OI	10 (6.3–17.7)	9.1 (6.0–14.3)	12.2 (6.7–24.2)	<0.001
$F_{I_{O_2}}$	0.60 (0.44–0.90)	0.50 (0.40–0.75)	0.79 (0.50–1.00)	<0.001
PEEP, cm H_2O	8.0 (6.0–10.0)	8.0 (6.6–10.0)	6.0 (5.0–10.0)	<0.001
Data over first 24 h (*n* = 974)				
PARDS severity				<0.001
PF > 300	113 (11)	92 (12.5)	21 (7.2)	
PF 200–300	400 (39)	341 (46.5)	59 (20.2)	
PF 100–200	405 (39.5)	264 (40)	141 (48.3)	
PF ⩽ 100	108 (10.5)	37 (5.1)	71 (24.3)	
PF category improved	387 (37.7)	281 (38.2)	106 (36.6)	0.8
Pa_{O_2}, mm Hg (*n* = 862)	89 (76–108)	89 (78–106)	89 (73–111)	0.49
Day 1 average Pa_{O_2} range	*n* = 862	*n* = 624	*n* = 238	<0.001
Pa_{O_2} ⩽ 60 mm Hg	40 (4.6)	19 (3)	21 (8.8)	
Pa_{O_2} 60–80 mm Hg	240 (27.8)	167 (26.8)	73 (30.7)	
Pa_{O_2} 80–100 mm Hg	300 (34.8)	246 (39.4)	54 (22.7)	
Pa_{O_2} > 100 mm Hg	282 (32.7)	192 (30.8)	90 (37.8)	
OI	7.6 (5.3–13.0)	7.0 (5.2– 10.5)	10.0 (5.4–19.3)	<0.001
$F_{I_{O_2}}$	0.47 (0.40–0.60)	0.44 (0.38–0.52)	0.61 (0.50–0.80)	<0.001
PEEP, cm H_2O	8.8 (6.7–10.8)	9.4 (8.0–10.9)	7.0 (5.0–10.0)	<0.001
V_T, ml/kg	7.5 (6.5–8.6)	7.7 (6.5–9.0)	7.5 (6.5–8.6)	0.50
PIP, cm H_2O	28 (24.5–33)	28 (24.6–32)	29.5 (24–34)	0.32
Driving pressure, cm H_2O	19.5 (16–23)	19 (15.6–22)	20.1 (17.2–25.5)	<0.001
Inotropes	598 (61.0)	446 (63.0)	152 (55.2)	0.02
Nitric oxide	195 (19.9)	132 (18.8)	63 (22.9)	0.14
Outcome				
Mortality	191 (18.2)	111 (14.9)	80 (26.5)	<0.001
28-day ventilator-free days	17.0 (0–22)	17.4 (3.0–22.1)	15.6 (0–21.2)	0.02

For definition of abbreviations, *see* Table 1.

Data are presented as median (interquartile range) or *n* (%). When a Pa_{O_2} metric was not available, PF was calculated from ratio of oxygen saturation measured by pulse oximetry to $F_{I_{O_2}}$, and OI was calculated from OSI using previously published formulae (19). A total of 1,047 patients had PEEP/$F_{I_{O_2}}$ data available for analysis. Race, ARDS triggers, and comorbidities were not available in the CPCCRN data, so the total number is reduced to 979. Some patients did not have available data 24 hours after PARDS diagnosis (died, extubated, or no PF ratio, OI, or OSI available), so the number is reduced to 974. Twenty-eight–day ventilator-free days defined as the number of days in the first 28 days after ARDS diagnosis in which the patient was alive and not on invasive mechanical ventilation. The percentages refer to the percent overall patients, high/on-protocol PEEP, or low PEEP with a given variable. *P* values are comparing the difference between two PEEP groups, among variables or groupings of variables (i.e., $P < 0.001$ for PARDS severity implies difference in PARDS severity categories between high/on-protocol PEEP and low PEEP without *post hoc* comparison of which groups are different).

patient-specific factors, we sought to identify variables that may be associated with use of lower PEEP. For this analysis, we restricted the cohort to the 1,047 patients with complete PEEP and F_{IO_2} values. Variables found to be associated with PEEP use lower than recommended by the protocol for a given F_{IO_2} (all $P < 0.05$) included Hispanic race, dataset, lower initial and 24-hour PF ratio and worse PF group, higher OI, lower use of inotropes, sepsis, higher Pediatric Risk of Mortality III score, and higher ventilator driving pressure (peak inspiratory pressure − PEEP). Age and V_T were not associated with PEEP lower than the protocol ($P > 0.2$). PF ratio group improved 24 hours after PARDS diagnosis in 38% of patients, although this did not appear to be related to PEEP use in relation to the protocol (Table 2).

Multivariable and Propensity Models

In general, more hypoxemic patients with higher severity of illness were more likely to be managed with lower PEEP relative to F_{IO_2} (Table 2). To account for these factors, we first constructed a multivariable logistic regression model on the outcome of PICU mortality. After controlling for PF ratio over the first 24 hours, inotrope use, immunodeficiency, stem cell transplant, Pediatric Risk of Mortality III score, nitric oxide, driving pressure, and dataset, patients managed with PEEP levels lower than recommended by the ARDSNet for a given F_{IO_2} were more likely to die (odds ratio [OR], 2.05; 95% confidence interval [CI], 1.32–3.17; Table 3). There were two significant multiplicative interactions that were included (CHOP dataset × nitric oxide and inotrope × stem cell transplant). The interaction between CHOP dataset and PEEP in relation to the protocol was not significant ($P = 0.4$). In addition, we created a propensity model for using PEEP lower than recommended by the protocol. Similarly, after adjusting for this propensity to use lower PEEP and other covariates, we found that lower PEEP relative to F_{IO_2} proposed in the ARDSNet model was independently associated with higher mortality (OR, 2.0; 95% CI, 1.24–3.22) (*see* Tables E1–E3 in the online supplement).

Sensitivity Analysis

When limiting the analysis to only those who had PF ratio less than or equal to 200

Table 3. Multivariable Model on ICU Mortality

Variable	Odds Ratio (95% CI)	*P* Value
PEEP lower than ARDSNet (vs. on-protocol/high PEEP)	2.05 (1.32–3.17)	0.001
PRISM III*	1.08 (1.06–1.11)	<0.001
Immunodeficiency (vs. no immunodeficiency)	2.00 (1.27–3.13)	0.003
Stem cell transplant, no inotropes	4.64 (2.29–9.39)	<0.001
Stem cell transplant, yes inotropes	12.4 (5.12–30.1)	0.013
No stem cell transplant, yes inotropes	2.67 (1.66–4.30)	<0.001
CHOP dataset (vs. all other datasets)	0.46 (0.28–0.77)	0.001
Nitric oxide not at CHOP	3.28 (1.70–6.35)	0.001
Nitric oxide at CHOP	1.29 (0.52–3.23)	NS
Driving pressure*	1.05 (1.009–1.087)	0.015
PF ratio (Day 1)*	1.0 (0.998–1.002)	0.91

Definition of abbreviations: ARDSNet = ARDS Network; CHOP = Children's Hospital of Philadelphia; CI = confidence interval; NS = not significant; PEEP = positive end-expiratory pressure; PF = Pa_{O_2}/F_{IO_2}; PRISM = Pediatric Risk of Mortality.

There was an independent association between PEEP lower than recommended by the ARDSNet protocol for a given F_{IO_2} and higher mortality, after controlling for PRISM III score, immunodeficiency, stem cell transplant, inotrope use, nitric oxide, driving pressure, PF ratio, and dataset. There were multiplicative interactions between inotrope use and stem cell transplant, and CHOP and nitric oxide use. PF ratio was retained in model because it had an important confounding effect on the relationship between PEEP lower than the protocol and mortality.

*Variables treated as continuous in the multivariable model.

Table 4. Children's Hospital of Philadelphia versus Children's Hospital Los Angeles Cohort Demographics, Comorbidities, Ventilator Management, and Outcomes among All Patients with Acute Respiratory Distress Syndrome

	CHLA (*N* = *612*)	CHOP (*N* = *453*)	*P* Value
Age, mo	46 (11.2 to 141)	49 (16.8 to 143)	0.16
ARDS trigger			
Pneumonia	361 (59)	299 (66)	0.02
Sepsis	225 (36.8)	98 (21.6)	<0.001
Neurological disease	165 (27)	95 (21)	0.02
Trauma	43 (7)	29 (6.4)	0.7
Drowning	9 (1.5)	11 (2.4)	0.255
Aspiration	28 (4.6)	54 (11.9)	<0.001
Comorbidities			
Immunodeficiency	161 (26.3)	87 (19)	0.007
Stem cell transplant	31 (5)	33 (7.3)	0.13
Cancer	100 (16.3)	61 (13.4)	0.19
Solid transplant	35 (5.7)	6 (1.3)	<0.001
PRISM III raw score	11 (6 to 17)	11 (5 to 17)	0.47
Day 1 ventilator settings			
F_{IO_2}	0.49 (0.41 to 0.65)	0.45 (0.37 to 0.56)	<0.0001
Mean airway pressure, cm H_2O	13.3 (10.2 to 17.7)	16 (14 to 19)	<0.0001
PEEP, cm H_2O	8.0 (6 to 10)	10 (8 to 11.4)	<0.0001
PF ratio	190 (128 to 258)	210 (162 to 251)	0.01
OI	6.6 (4.4 to 11.8)	8.4 (6.2 to 13.5)	<0.0001
Driving pressure, cm H_2O	19.5 (16 to 22.5)	19.5 (16 to 23.5)	0.18
V_T, ml/kg	7.6 (6.2 to 9.1)	7.4 (6.6 to 8.2)	0.06
PEEP discordance	0 (−2 to 0)	2 (0 to 3)	<0.0001
Low	222 (40.2)	53 (12.4)	<0.0001
On	196 (35.3)	123 (28.8)	
High	134 (24.3)	251 (58.8)	
Inotropes or vasopressors	270 (44.1)	360 (79)	<0.0001
Nitric oxide	62 (10.1)	161 (35)	<0.0001
Outcomes			
Mortality	137 (22.4)	65 (14.4)	0.001
28-day VFDs	16.7 (0 to 23)	16 (3 to 21)	0.01

Definition of abbreviations: ARDS = acute respiratory distress syndrome; CHLA = Children's Hospital Los Angeles; CHOP = Children's Hospital of Philadelphia; IQR = interquartile range; OI = oxygenation index; PEEP = positive end-expiratory pressure; PF = Pa_{O_2}/F_{IO_2}; PRISM = Pediatric Risk of Mortality; VFD = ventilator-free days.

Data are presented as median (IQR) and *n* (%). *See* online supplement for subgroups by PF ratio.

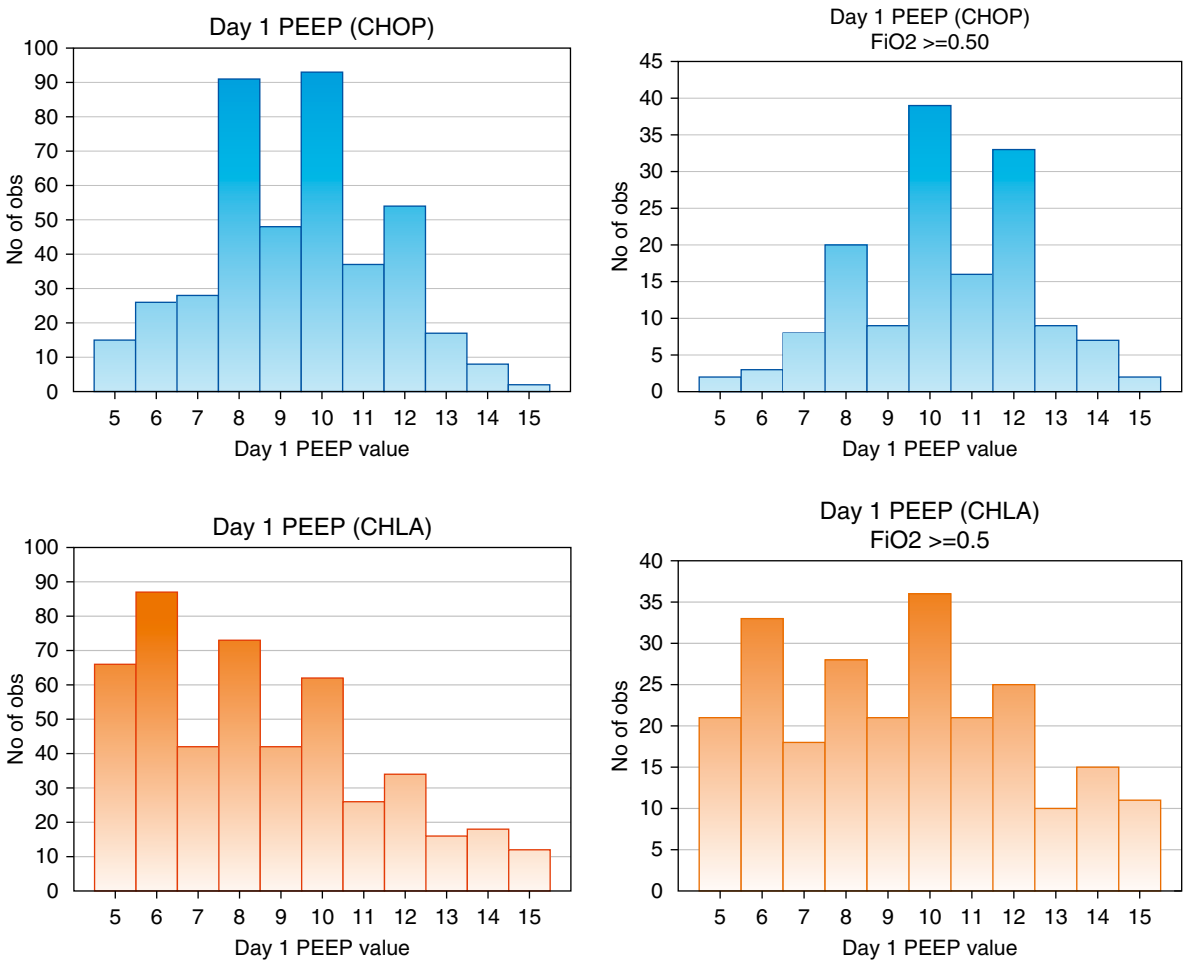

Figure 4. Positive end-expiratory pressure (PEEP) distribution for Children's Hospital of Philadelphia (CHOP) (blue, top) versus Children's Hospital Los Angeles (CHLA) (orange, bottom). There is a relatively normal distribution of PEEP in the CHOP dataset, which is shifted slightly to the right when $F_{I_{O_2}}$ is increased over 0.5 (top right). In contrast, CHLA data have more variability in PEEP, which is retained, although shifted to the right, when $F_{I_{O_2}}$ is increased over 0.5 (bottom right). obs = observations.

24 hours after PARDS diagnosis, the multivariable OR was similar, although no longer statistically significant (OR, 1.64; 95% CI, 0.97–2.77; $P = 0.06$).

There were notable differences among the datasets, which prompted us to perform subgroup analysis and directly compare CHOP and CHLA patients. CHLA had a higher percentage of patients with initial PF ratio less than 100 (33% CHLA vs. 23% CHOP, $P < 0.001$). PF ratio improved in a similar percentage of patients by 24 hours between datasets (36% CHLA vs. 39% CHOP, $P = 0.4$). By 24 hours into PARDS diagnosis, 14.6% of patients at CHLA had PF less than 100 compared with 6.6% at CHOP ($P < 0.001$). Patients at CHOP were more likely to be on inotropes and vasopressors or have pneumonia or aspiration. Patients at CHLA were more likely to have sepsis, immunodeficiency, and solid organ transplant (Table 4, all $P < 0.05$; stratified by PF, Table E4).

Regarding ventilator management, CHOP used higher PEEP when $F_{I_{O_2}}$ was between 0.21 and 0.6 compared with CHLA (Figures E1A–E1D). PEEP at CHOP follows a near-normal distribution, whereas PEEP at CHLA has more variability (Figure 4). CHOP used PEEP lower than protocol only 12.4% of the time (79% PF < 100; 17.5% PF 100–200; 2.9% PF 200–300), compared with 40% at CHLA (63% PF < 100; 45.1% PF 100–200; 28.4% PF 200–300). As a result, patients with PF ratio greater than 100 24 hours after PARDS diagnosis at CHOP were on a higher mean airway pressure, higher PEEP, and had a higher OI, with similar or higher PF ratio. CHOP patients were more likely to be on inhaled nitric oxide (97% PF < 100; 51% PF 100–200; 20% PF 200–300) than CHLA patients (26% PF < 100; 10% PF 100–200; 5% PF 200–300). Driving pressure and V_T were similar between CHOP and CHLA (Figures 5 and E2 and Tables 4 and E4).

Nonconventional ventilation (NCV) strategies were used in 24.7% of patients within the first 24 hours of PARDS diagnosis at CHOP, compared with 9.6% at CHLA ($P < 0.001$). The median OI at initiation of NCV was 20 (IQR, 15–28), with a median PEEP of 12 (IQR, 10–12) at CHOP compared with a median OI of 35 (IQR, 18–48) with a median PEEP of 14 (IQR, 10–15) at CHLA (both $P < 0.01$). Mortality was similar between those who did and did not receive NCV within the first 24 hours at CHOP (14.3% vs. 14.4%, $P = 0.99$), but those who received NCV within the first 24 hours at CHLA had much higher mortality (44% vs. 18.9%, $P < 0.001$). At

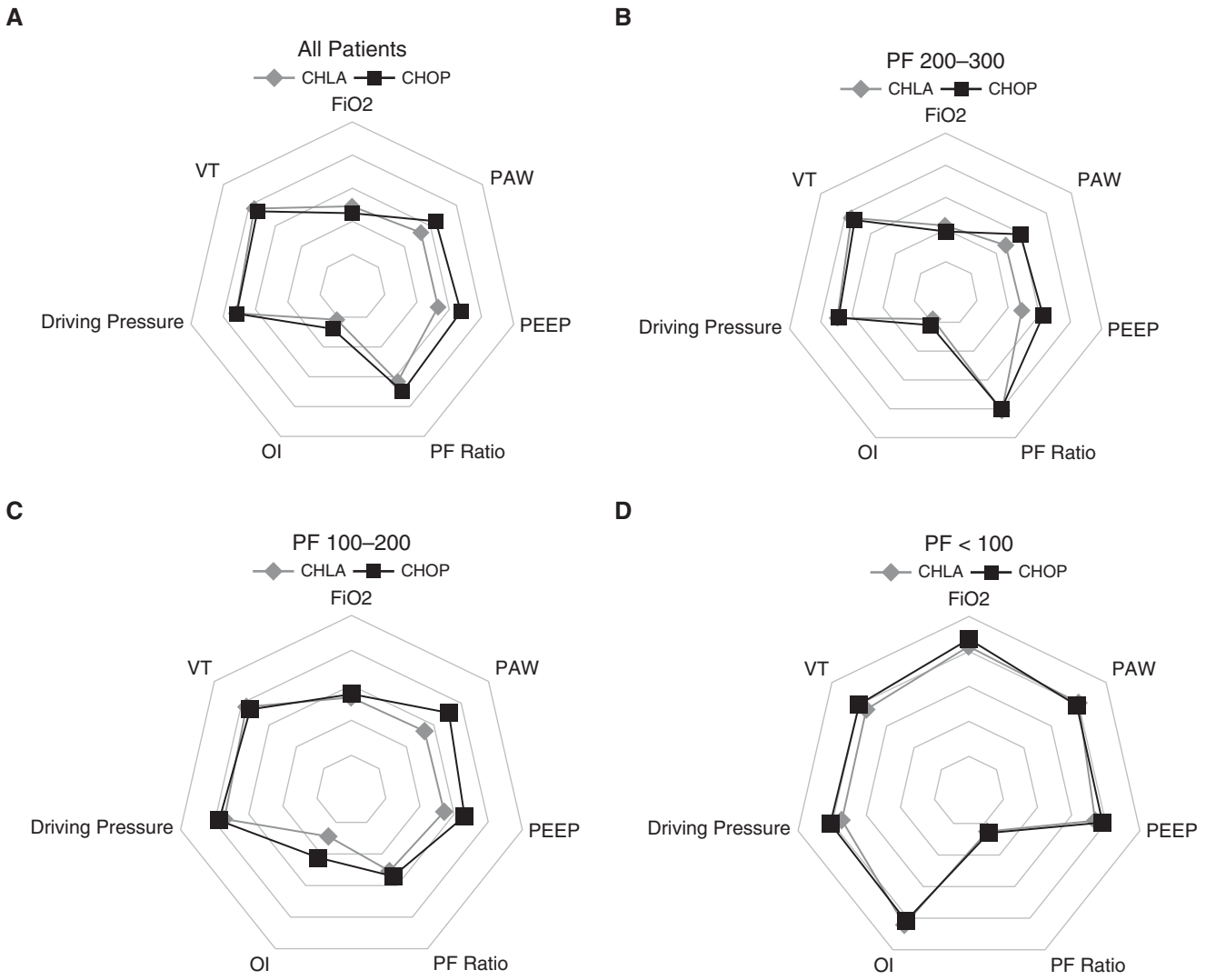

Figure 5. Differences in ventilator strategy on Day 1 of acute respiratory distress syndrome (ARDS) between Children's Hospital of Philadelphia (CHOP) and Children's Hospital Los Angeles (CHLA), stratified by $Pa_{O_2}/F_{I_{O_2}}$ (PF) ratio 24 hours after pediatric ARDS (PARDS) diagnosis. All variables are scaled to a maximum value of 1 for each variable, to highlight relative differences between datasets. Actual values for these parameters can be found in Tables 4 and E4. The individual squares and diamonds represent the median value for the dataset for a given variable. (*A*) For all patients, CHOP generally used a higher mean airway pressure (PAW), higher positive end-expiratory pressure (PEEP), and slightly lower $F_{I_{O_2}}$ than CHLA, with slightly higher PF ratio and oxygenation index (OI), and similar driving pressure and V_T. (*B* and *C*) For patients with PF ratio (*B*) 200 to 300 or (*C*) 100 to 200, PAW and PEEP are higher at CHOP than CHLA. (*D*) For those with PF less than or equal to 100, PAW, PEEP, OI, and PF ratio are similar between datasets, although $F_{I_{O_2}}$, V_T, and driving pressure are slightly higher at CHOP.

CHOP, the first NCV mode was airway pressure release ventilation in 12.9%, extracorporeal membrane oxygenation in 1.3%, high-frequency oscillatory ventilation in 43%, and high-frequency percussive ventilation in 43%. High-frequency oscillatory ventilation was the first NCV mode used at CHLA in all patients.

On a univariate basis in both institutions, PEEP lower than protocol on Day 1 was associated with higher mortality (Figure E3). This relationship was retained in the CHLA cohort after controlling for potential confounding factors (OR, 2.09; 95% CI, 1.26–3.46; Table 5). However, after controlling for confounding factors in the CHOP dataset, PEEP lower than the protocol was not associated with mortality (OR, 0.87; 95% CI, 0.32–2.35; Table 6).

Day 2 and 3 PEEP data were available from the CHLA dataset, and the multivariable odds ratios were similar, although findings were not statistically significant, likely because of smaller sample size (Tables E5 and E6).

Discussion

Using the ARDSNet PEEP/$F_{I_{O_2}}$ protocol as a framework to analyze observational data from more than 1,100 patients with PARDS, we have found that patients managed with PEEP levels lower than recommended by the ARDSNet model for a given $F_{I_{O_2}}$ had higher mortality. This is consistent when stratifying by PF ratio and holds after controlling for confounding variables directly in multivariable modeling, as well as in propensity-based covariate adjustment.

Table 5. Children's Hospital Los Angeles Patients Only, Multivariable Model for ICU Mortality Including Data from Day 1 of Mechanical Ventilation ($n = 535$)

Variable	Odds Ratio (95% CI)	*P* Value
PEEP lower than ARDSNet (vs. on-protocol/high PEEP)	2.09 (1.26–3.46)	0.004
PRISM III*	1.08 (1.05–1.11)	<0.001
Immunodeficiency (vs. no immunodeficiency)	2.71 (1.19–6.21)	0.018
Stem cell transplant, no inotrope	4.97 (2.49–9.95)	0.001
Stem cell transplant, yes inotrope	16.00 (3.3–77.1)	<0.001
No stem cell transplant, yes inotrope	2.23 (1.40–3.56)	0.001
Nitric oxide (vs. no nitric oxide)	3.37 (1.70–6.64)	<0.001
Driving pressure*	1.07 (1.02–1.12)	0.009
PF ratio (Day 1)*	1.001 (0.998–1.004)	0.42

Definition of abbreviations: ARDSNet = ARDS Network; CI = confidence interval; PEEP = positive end-expiratory pressure; PF = $Pa_{O_2}/F_{I_{O_2}}$; PRISM = Pediatric Risk of Mortality.
PEEP lower than recommended by the ARDS Network Protocol for a given $F_{I_{O_2}}$ remains independently associated with mortality.
*Variables treated as continuous in the multivariable model.

Although we chose to combine datasets for the primary analysis using interaction terms to account for differences among the institutions, notable differences in comorbidities and ventilator management between datasets prompted us to perform subgroup analysis stratified by institution, namely CHOP and CHLA. The sensitivity analysis highlights that the relationship between PEEP lower than the protocol and mortality is most relevant in the CHLA data. We believe this is for several reasons. *1*) CHOP patients are generally managed with PEEP in line with or higher than recommended by the protocol. Only 12% of patients have PEEP levels lower than recommended by the protocol at CHOP, compared with 40% at CHLA and 40% in the CPCCRN dataset. This resulted in higher PEEP and mean airway pressure for a similar PF ratio. *2*) PEEP use does not vary as much at CHOP as a function of hypoxemia severity. At CHOP, nearly all patients with PF ratio greater than 100 had PEEP above protocol, and nearly all patients with PF less than 100 had PEEP below protocol. These extremes (<20% of patients below protocol when PF > 100 and 20% on or above protocol when PF < 100) make it difficult to draw conclusions about PEEP management from the CHOP dataset alone, because using observational data to compare outcomes of patients who are managed with different PEEP/$F_{I_{O_2}}$ combinations is dependent on variability in PEEP level for a given $F_{I_{O_2}}$. This variability was present in CHLA and CPCCRN datasets, but not at CHOP. *3*) Patients at CHOP were three to four times more likely to receive inhaled nitric oxide than those at CHLA, which may also alter hypoxemia severity. *4*) CHOP uses nearly three times more NCV in the first 24 hours than CHLA, with a median OI of 20 at initiation of NCV at CHOP, compared with 35 at CHLA. *5*) CHOP primarily uses pressure-regulated volume control, whereas CHLA uses primarily pressure control, although V_T and driving pressure were similar between datasets. *6*) Finally, CHOP included only patients with bilateral infiltrates on chest imaging, whereas the other datasets included patients with unilateral or bilateral disease. We chose not to stratify analysis on the basis of chest imaging interpretation, because each dataset used different methods for gauging bilateral versus unilateral disease (i.e., radiologist, intensivist, multiple practitioners, and timing of the films). Future studies need to standardize these interpretations before we understand their relevance.

Table 6. Children's Hospital of Philadelphia Patients Only, Multivariable Model for ICU Mortality Including Data from Day 1 of Mechanical Ventilation ($n = 427$)

Variable	Odds Ratio (95% CI)	*P* Value
PEEP lower than ARDSNet (vs. on-protocol/high PEEP)	0.87 (0.32–2.35)	0.78
PRISM III*	1.10 (1.07–1.14)	<0.001
Immunodeficiency (vs. no immunodeficiency)	2.80 (1.26–6.24)	0.012
Stem cell transplant (vs. no stem cell transplant)	4.70 (1.69–13.2)	0.003
PF ratio (Day 1)*	0.995 (0.989–1.0001)	0.06

For definition of abbreviations, *see* Table 5.
PEEP lower than recommended by the ARDS Network Protocol for a given $F_{I_{O_2}}$ did not remain independently associated with mortality after multivariable adjustment.
*Variables treated as continuous in the multivariable model.

Overall mortality was lower at CHOP than CHLA. Part of this relates to different inclusion criteria and methods for screening for PARDS, different PARDS triggers, differences in comorbidities between datasets, and differences in adjuvant therapies, such as inhaled nitric oxide and inotropes and vasopressors. However, ventilator strategies between institutions were similar with respect to V_T and driving pressure but were notably different with oxygenation strategies (particularly higher PEEP at CHOP for those with mild or moderate ARDS and sooner transition to alternative modes of ventilation rather than further escalating PEEP for severe ARDS). These data highlight a reality of multicenter practice and research, that ventilator management is institution and practitioner dependent in the absence of an agreed-on protocol. There are few validated pediatric protocols, making this an important area for research. PEEP management at CHOP is less variable than CHLA, with significantly fewer patients managed with PEEP lower than recommended by ARDSNet (12% vs. 40%). These findings may contribute to the mortality differences between datasets.

Our findings could have significant implications. As our data and previous investigations have highlighted (2, 8, 9, 11), there is reluctance among pediatric intensivists to escalate PEEP in response to hypoxemia, preferentially increasing $F_{I_{O_2}}$. On average, PEEP plateaus around 10 cm H_2O, even with severe hypoxemia. The reasons are likely multifactorial and may relate to concerns about high PEEP levels in infants and neonates with low chest wall elastance, concerns about

cardiopulmonary interactions, or a belief that high $F_{I_{O_2}}$ is not dangerous (20, 21). Interestingly, we found that patients with hyperoxia (i.e., $Pa_{O_2} > 100$ mm Hg) had higher mortality than those with more normal Pa_{O_2} (60–100 mm Hg, Table 1), although this finding did not hold in multivariable modeling. However, it provides indirect evidence of ill effects of high concentrations of oxygen, particularly if it leads to hyperoxia. Although the general principles of lung-protective ventilation with use of higher PEEP to promote alveolar recruitment are supported among pediatric intensivists, and in fact specifically recommended in expert-based guidelines for PARDS management (1, 10, 22, 23), our data highlight that these principles are not executed at the bedside for most children.

In truth, there are no clear data that demonstrate that PEEP level matters in PARDS. There have been no randomized controlled trials and, like many other pieces of ventilator management in ARDS, direct extrapolation from adults has limitations (3, 15, 20, 24–27). In our analysis, for patients with initially similar levels of hypoxemia, management with PEEP that is escalated in conjunction with $F_{I_{O_2}}$ is associated with lower mortality than those for whom $F_{I_{O_2}}$ is primarily increased. Interestingly we found this pattern most evident in those with moderate hypoxemia (PF, 100–200). Although one could speculate as to physiologic reasons for this finding, it likely relates to sample size and variability in PEEP management in this range. The range of PEEP (below, on protocol, and higher than protocol) is well represented in this subgroup, making it more possible to find a relationship. A large proportion of patients with PF less than 100 were managed with PEEP below the protocol, and many were transitioned to alternative modes of ventilation, making it difficult to draw conclusions in this group specifically.

However, our observational data cannot and should not imply a causal relationship that management on the basis of the ARDSNet PEEP/$F_{I_{O_2}}$ table for PARDS would result in improved mortality, although there is strong biological plausibility for this (6). Moreover, there are many reasons to believe that the ARDSNet PEEP/$F_{I_{O_2}}$ table is suboptimal in PARDS, as a more individualized approach using transpulmonary pressure, lung compliance, dead space, or other methods have strong theoretical advantages (5, 6, 28–34). Nevertheless, our data do highlight that there may be problems with usual care PEEP management in PARDS and that clinical trials in this area should be a priority for research. This is particularly important in light of the recent findings from the Alveolar Recruitment for ARDS Trial (ART), that adult patients with ARDS managed with lung recruitment and PEEP titration on the basis of respiratory system compliance had higher mortality than those managed with the ARDSNet PEEP/$F_{I_{O_2}}$ protocol (35).

We are limited by the data available, and it may be that our findings reflect patient severity of illness or residual unmeasured confounding. Because of the nature of the ARDSNet PEEP/$F_{I_{O_2}}$ titration model, patients with very negative PEEP discordance values must be on high levels of $F_{I_{O_2}}$. Indeed, the largest proportion of patients who were managed with lower PEEP relative to the amount of $F_{I_{O_2}}$ had severe hypoxemia. To mitigate these concerns, we performed a variety of stratified analyses as well as two methods for adjustment and multivariable modeling. Our findings held after multivariable and propensity covariate adjustment incorporating oxygenation metrics, PARDS triggers, comorbidities, inotropes and vasopressors, admission severity of illness, other ventilator settings, and inhaled nitric oxide. However, we did not have data on other potential confounders (i.e., other cointerventions like neuromuscular blockade, prone positioning, air leak syndrome or pneumothorax, etc.), and there is potential selection bias on the basis of individual practices for arterial line placement and potential differences on the basis of bilateral versus unilateral infiltrates. These limitations can likely only be overcome with a well-designed randomized control trial.

In conclusion, through secondary analysis of data from more than 1,100 patients with PARDS, we have found that patients managed with PEEP levels lower than recommended by the ARDSNet PEEP/$F_{I_{O_2}}$ model experienced higher mortality, even after covariate adjustment. Randomized controlled trials targeting PEEP management in PARDS are needed. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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