Characterizing Degree of Lung Injury in Pediatric Acute Respiratory Distress Syndrome

Nadir Yehya, MD[1]; Sabah Servaes, MD[2]; Neal J. Thomas, MD, MSc[3]

Objective: Although all definitions of acute respiratory distress syndrome use some measure of hypoxemia, neither the Berlin definition nor recently proposed pediatric-specific definitions proposed by the Pediatric Acute Lung Injury Consensus Conference utilizing oxygenation index specify which Pao_2/Fio_2 or oxygenation index best categorizes lung injury. We aimed to identify variables associated with mortality and ventilator-free days at 28 days in a large cohort of children with acute respiratory distress syndrome.

Design: Prospective, observational, single-center study.

Setting: Tertiary care, university-affiliated PICU.

Patients: Two-hundred eighty-three invasively ventilated children with the Berlin-defined acute respiratory distress syndrome.

Interventions: None.

Measurements and Main Results: Between July 1, 2011, and June 30, 2014, 283 children had acute respiratory distress syndrome with 37 deaths (13%) at the Children's Hospital of Philadelphia. Neither initial Pao_2/Fo_2 nor oxygenation index at time of meeting acute respiratory distress syndrome criteria discriminated mortality. However, 24 hours after, both Pao_2/Fio_2 and oxygenation index discriminated mortality (area under receiver operating characteristic curve, 0.68 [0.59–0.77] and 0.66 [0.57–0.75]; $p < 0.001$). Pao_2/Fio_2 at 24 hours categorized severity of lung injury, with increasing mortality rates of 5% (Pao_2/Fio_2, > 300), 8% (Pao_2/Fio_2, 201–300), 18% (Pao_2/Fio_2, 101–200), and 37% (Pao_2/Fio_2, ≤ 100) across worsening Berlin categories. This trend with 24-hour Pao_2/Fio_2 was seen for ventilator-free days (22, 19, 14, and 0 ventilator-free days across worsening Berlin categories; $p < 0.001$) and duration of ventilation in survivors (6, 9, 13, and 24 d across categories; $p < 0.001$). Similar results were obtained with 24-hour oxygenation index.

Conclusions: Pao_2/Fio_2 and oxygenation index 24 hours after meeting acute respiratory distress syndrome criteria accurately stratified outcomes in children. Initial values were not helpful for prognostication. Definitions of acute respiratory distress syndrome may benefit from addressing timing of oxygenation metrics to stratify disease severity. (*Crit Care Med* 2015; 43:937–946)

Key Words: acute respiratory distress syndrome; oxygenation index; Pao_2/Fio_2; pediatric

*See also p. 1130.

[1]Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA.

[2]Department of Radiology, Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA.

[3]Division of Pediatric Critical Care Medicine, Department of Pediatrics and Public Health Science, Penn State Hershey Children's Hospital, Hershey, PA.

This study was performed at Children's Hospital of Philadelphia.

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For information regarding this article, E-mail: yehyan@email.chop.edu

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In neither the 1994 American-European Consensus Conference (AECC) (1) nor the 2012 Berlin definitions (2) of acute respiratory distress syndrome (ARDS) were pediatric considerations addressed. Absent such, AECC and Berlin definitions are applied to children without modification, despite the different epidemiology and outcomes of pediatric ARDS (PARDS) (3–6). To address this, the Pediatric Acute Lung Injury and Sepsis Investigators sponsored the Pediatric Acute Lung Injury Consensus Conference (PALICC) (7) to propose definitions for PARDS. Notable differences in the PALICC definition are use of oxygenation index (OI) instead of Pao_2/Fio_2, alternative stratification based on Spo_2 rather than Pao_2 (oxygen saturation index) (8, 9), and less restrictive radiographic criteria (10).

Common to all ARDS definitions is reliance on some measure of hypoxemia as a marker for lung injury. However, specifically when clinicians should measure this value for ARDS risk stratification is unclear. Pao_2/Fio_2 is susceptible to ventilator settings (11, 12), venous admixture (13), and Fio_2 (14, 15). OI similarly changes with ventilator management and response to treatment (3). The Berlin definition does not specify when

TABLE 1. Characteristics of Acute Respiratory Distress Syndrome Population (*n* = 283)

Variable	Values[a]
Age (yr)	4.1 (1.4, 12.8)
Female/male (%/%)	118/165 (42/58)
Ethnicity (%)	
Asian	5 (2)
Black	92 (32)
Hispanic/Latino	33 (12)
White	124 (44)
Other	29 (10)
Pediatric Risk of Mortality III at 12 hr	10 (5, 17)
Comorbidities	
Genetic syndrome	41 (15)
Prematurity	39 (14)
Static encephalopathy	35 (12)
Oncologic condition	38 (13)
Stem cell transplant	20 (7)
Other comorbidity	19 (7)
Immunocompromised condition (%)	54 (19)
Cause of ARDS	
Infectious pneumonia	164 (58)
Aspiration pneumonia	28 (10)
Sepsis	51 (18)
Trauma	22 (8)
Other	18 (6)
Nonpulmonary organ dysfunctions at ARDS onset	2 (1, 3)
Vasopressor use in the first 72 hr	
Maximum number of concurrent vasopressor infusions	1 (1, 2)
Maximum vasopressor score	10 (4, 20)
Ancillary therapies in the first 72 hr	
Change to airway pressure release ventilation, high-frequency oscillatory ventilation, or high-frequency percussive ventilation	99 (35)
Continuous neuromuscular blockade	131 (46)
Inhaled nitric oxide	105 (37)
Surfactant	6 (2)
Prone positioning	5 (2)
ARDS onset	
Pao_2/Fio_2	156 (110, 205)
OI	10.2 (7.1, 16.3)
Fio_2	0.50 (0.45, 0.80)
Positive end-expiratory pressure (cm H_2O)	10 (8, 12)
Peak inspiratory pressure (cm H_2O)	30 (25, 35)
Mean airway pressure (cm H_2O)	16 (14, 18)
Exhaled V_T (mL/kg actual body weight)	7.5 (6.7, 8.3)
24 hr after ARDS onset	
Pao_2/Fio_2	222 (165, 274)
OI	6.9 (5.2, 10.5)
Fio_2	0.40 (0.35, 0.50)
Positive end-expiratory pressure (cm H_2O)	10 (8, 10)
Peak inspiratory pressure (cm H_2O)	27 (24, 32)
Mean airway pressure (cm H_2O)	15 (14, 19)
Exhaled V_T (mL/kg actual body weight)	7.3 (6.5, 8.1)
Transition to extracorporeal membrane oxygenation at any time	13 (5)
Outcomes	
Duration of mechanical ventilation (d)	10 (6, 17)
Duration of PICU stay (d)	15 (9, 26)
Ventilator-free days at 28 d (d)	17 (3, 21)
PICU mortality, nonsurvivors (%)	37 (13)

ARDS = acute respiratory distress syndrome, OI = oxygenation index, V_T = tidal volume.

[a]Data are presented as median (interquartile range) or number (%).

the diagnostic/prognostic Pao_2/Fio_2 should be measured during ARDS; PALICC suggests measuring OI at PARDS onset and at 24, 48, and 72 hours after, without comment regarding superiority.

This study, initiated in 2011 prior to publication of either Berlin or PALICC, prospectively collected data on mechanically ventilated children with Pao_2/Fio_2 up to 300 with acute lung injury (ALI, AECC definition) to identify risk factors associated with mortality and ventilator-free days (VFDs) at 28 days. Given prior studies have demonstrated limited utility of initial oxygenation defects (3, 11), we hypothesized that metrics of hypoxemia (Pao_2/Fio_2 or OI) would be more useful for risk stratification when collected 24 hours after meeting ARDS criteria, rather than at ARDS onset.

METHODS

Study Design and Patient Selection

This prospective, observational study was approved by the Children's Hospital of Philadelphia's (CHOP) Institutional Review Board, and requirement for informed consent waived. As AECC (and Berlin) definitions of ARDS rely on invasive measures of oxygenation, only patients with arterial access were screened.

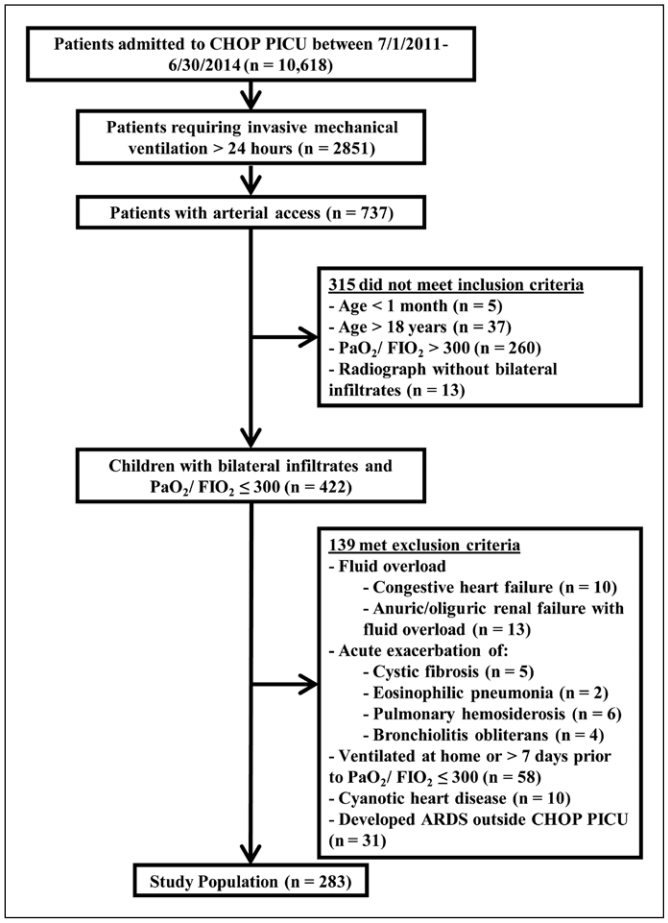

Figure 1. Flowchart for patient screening and eligibility. CHOP = Children's Hospital of Philadelphia.

TABLE 2. Performance of Oxygenation Metrics for Mortality

Variable Tested	Mortality Area Under the Curve (95% CI)[a]	p
Initial Pao_2/Fio_2	0.580 (0.480–0.680)	0.116
24-hr Pao_2/Fio_2	0.684 (0.594–0.774)	< 0.001
Worst Pao_2/Fio_2 in the first 24 hr	0.691 (0.611–0.771)	< 0.001
Initial OI	0.581 (0.472–0.689)	0.114
24-hr OI	0.661 (0.573–0.749)	0.002
Worst OI in the first 24 hr	0.661 (0.578–0.743)	0.002

OI = oxygenation index.

[a]Receiver operating characteristic curves were constructed using dummy variables for Berlin (PaO_2/FIO_2) and Pediatric Acute Lung Injury Consensus Conference (OI) oxygenation categories.

Consecutive patients in the PICU were screened daily for AECC-defined ALI and study eligibility between July 1, 2011, and June 30, 2014. Inclusion criteria were 1) acute respiratory failure requiring invasive (via endotracheal tube or tracheostomy) mechanical ventilation projected to last more than 24 hours, 2) invasive arterial access, 3) age older than 1 month (to avoid confounding by neonatal physiology) or younger than 18

TABLE 3. Performance of Oxygenation Metrics for Ventilator-Free Days = 0 or Ventilator-Free Days ≤ 14 Days

Variable Tested	VFD = 0 at 28 D AUC (95% CI)[a]	p	VFD ≤ 14 D AUC (95% CI)[a]	p
Initial Pao_2/Fio_2	0.591 (0.513– 0.669)	0.027	0.545 (0.401–0.608)	0.201
24-hr Pao_2/Fio_2	0.695 (0.627–0.764)	< 0.001	0.671 (0.611–0.732)	< 0.001
Worst Pao_2/Fio_2 in the first 24 hr	0.664 (0.595–0.733)	< 0.001	0.601 (0.540–0.662)	0.004
Initial OI	0.598 (0.519–0.677)	0.017	0.563 (0.499–0.627)	0.072
24-hr OI	0.678 (0.610–0.746)	< 0.001	0.678 (0.619–0.737)	< 0.001
Worst OI in the first 24 hr	0.645 (0.575–0.715)	< 0.001	0.608 (0.545–0.670)	0.002

VFD = ventilator-free days, AUC = area under the curve, OI = oxygenation index.

[a]Receiver operating characteristic curves were constructed using dummy variables for Berlin (PaO_2/FIO_2) and Pediatric Acute Lung Injury Consensus Conference (OI) oxygenation categories.

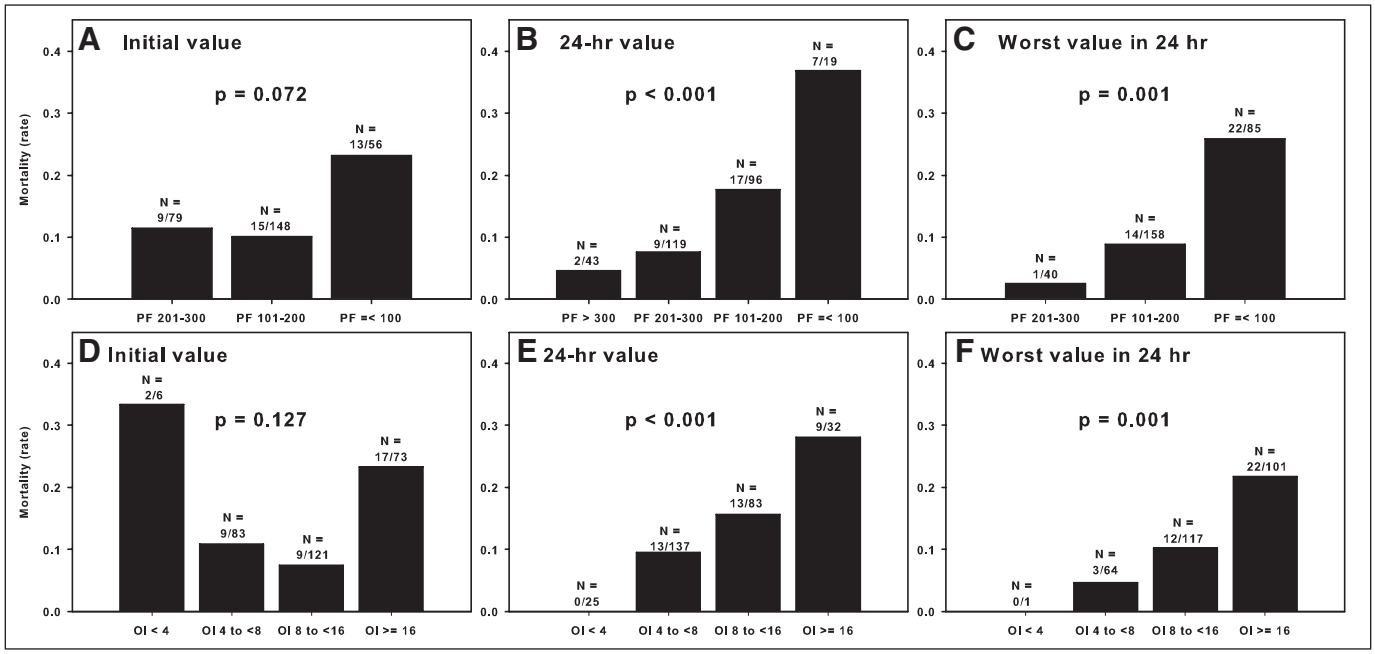

Figure 2. Classification of patients into Berlin (**A**–**C**) and Pediatric Acute Lung Injury Consensus Conference (**D**–**F**) oxygenation categories based on initial Pao_2/Fio_2 (PF) (A) or oxygenation index (OI) (D) at time of acute respiratory distress syndrome diagnosis, the value 24 hr after diagnosis (B and E), and the worst value in the first 24 hr (C and F). Mortality is plotted for each group. *p* Values represent a nonparametric test for trend, testing if mortality increases across worsening oxygenation categories.

years, 4) Pao_2/Fio_2 up to 300 on two consecutive arterial blood gases separated by at least 1 hour, and 5) bilateral parenchymal infiltrates on radiograph. Exclusion criteria were 1) respiratory failure from cardiac failure (determined by echocardiography) or fluid overload, 2) exacerbation of underlying chronic respiratory disease, 3) chronic ventilator dependence, 4) mixing cyanotic heart disease, 5) mechanical ventilation for more than 7 days before Pao_2/Fio_2 up to 300, and 6) ARDS established outside of the CHOP PICU. Determination of bilateral infiltrates was made independently by a blinded PICU attending and a blinded pediatric radiologist; only cases agreed to by both as consistent with ARDS met inclusion. Determination of hydrostatic pulmonary edema (from either heart failure or anuric/oliguric renal failure) as the sole etiology of respiratory failure was made in consultation with the PICU attending using available data. As the study was initiated prior to Berlin definitions of ARDS, we did not specify a minimum positive end-expiratory pressure (PEEP); however, our institutional practice does not use PEEP less than 5 cm H_2O, and all patients therefore met Berlin criteria for ARDS.

Data Collection and ARDS Management

Demographics, ventilator settings, laboratory data, and medications were recorded for the first 3 days of ARDS. We recorded first qualifying values (after initiation of ventilation) of Pao_2/Fio_2 and OI at ARDS diagnosis, 24 hours after diagnosis, and worst values in the first 24 hours. Ventilator settings were recorded at ARDS diagnosis and 24 hours afterward.

Absent a standardized ventilator protocol, our institutional practice is to initiate conventional ventilation with a minimum 5 cm H_2O of PEEP and attempt to wean Fio_2 to up to 0.60. There is no specific target Pao_2, but typically Pao_2 at least 60 mm Hg is accepted as long as there is clinical stability. Inability to wean Fio_2 prompts PEEP escalation and subsequent efforts to wean Fio_2, attempting to maintain peak inspiratory pressures (PIP) up to 35 cm H_2O. We exclusively use decelerating flow during conventional ventilation (either pressure control or pressure-regulated volume control). Persistently elevated PIP (≥ 35 cm H_2O), ongoing hypercarbia ($Paco_2 \geq 80$), or oxygenation difficulties (inability to wean $Fio_2 \leq 0.60$ despite increasing PEEP) prompted consideration for changing mode of ventilation or escalating to extracorporeal membrane oxygenation (ECMO). There was no standardization of ancillary therapies (inhaled nitric oxide [iNO], surfactant, neuromuscular blockade, and prone positioning), which was left to the discretion of the attending physician.

Equations and Definitions

Metrics of oxygenation used were Pao_2/Fio_2 and OI ((mean airway pressure [mPaw] × Fio_2 × 100)/Pao_2). The vasopressor score (16, 17) is as follows: dopamine dose (μg/kg/min) × 1 + dobutamine (μg/kg/min) × 1 + epinephrine (μg/kg/min) × 100 + norepinephrine (μg/kg/min) × 100 + phenylephrine (μg/kg/min) × 100 + milrinone (μg/kg/min) × 10. Extrapulmonary organ failures at time of ARDS diagnosis were identified using accepted definitions in children (18). The designation of "immunocompromised" required presence of an immunocompromising diagnosis (oncologic, immunologic, rheumatologic, or transplant) and active immunosuppressive chemotherapy or a congenital immunodeficiency (19). Severity-of-illness score used is the Pediatric Risk of Mortality (PRISM) III at 12 hours.

TABLE 4. Predictive Validity of 24-Hour Pao_2/FIO_2 and Worst Pao_2/FIO_2 in the First 24 Hours

	24-Hr Pao_2/FIO_2[a]				Worst Pao_2/FIO_2 in 24 Hr[b]		
Variable	> 300	201–300	101–200	≤ 100	201–300	101–200	≤ 100
Number of patients	43	119	96	19	40	158	85
Mortality (%) (95% CI)	2 (5) (1–14)	9 (8) (4–13)	17 (18) (11–26)	7 (37) (18–59)	1 (3) (0–11)	14 (9) (5–14)	22 (26) (17–36)
VFD 0 at 28 d (%) (95% CI)	2 (5) (1–14)	19 (16) (10–23)	29 (30) (22–40)	11 (68) (36–78)	4 (10) (3–22)	26 (16) (11–23)	34 (40) (30–51)
VFD ≤ 14 d (%) (95% CI)	8 (19) (9–32)	39 (33) (25–42)	48 (50) (40–60)	16 (84) (64–95)	13 (33) (20–48)	54 (34) (27–42)	48 (56) (46–67)
VFDs, median (IQR)	22 (16, 23)	19 (9, 22)	14 (0, 19)	0 (0, 10)	18 (12, 23)	19 (9, 21)	7 (0, 18)
Ventilator days in survivors, median (IQR)	6 (5, 11)	9 (6, 15)	13 (8, 19)	24 (14, 42)	10 (5, 16)	9 (6, 15)	12 (9, 24)

VFD = ventilator-free days, IQR = interquartile range.

[a]Comparisons of mortality, VFD = 0 at 28 d, VFD ≤ 14 d, VFDs, and ventilator days in survivors across Berlin categories using 24-hr PaO_2/FIO_2 were all statistically significant ($p < 0.001$).

[b]Comparisons of mortality ($p = 0.001$), VFD = 0 at 28 d ($p < 0.001$), VFD ≤ 14 d ($p = 0.002$), VFDs ($p < 0.001$), and ventilator days in survivors ($p = 0.007$) across Berlin categories using the worst PaO_2/FIO_2 in the first 24 hr were all statistically significant.

Reported outcomes are PICU mortality, VFDs at 28 days, and duration of mechanical ventilation. All mention of "mechanical ventilation" in this study implied "invasive" ventilation, and noninvasive support was not counted toward VFDs or total ventilator days. For VFDs and duration of mechanical ventilation, the first day was initiation of invasive ventilation. Liberation from invasive ventilation for more than 24 hours defined duration of mechanical ventilation. Patients requiring reinitiation of invasive ventilation after 24 hours of extubation had the extra days counted toward total ventilator days. VFDs were determined by subtracting total ventilator days from 28 in survivors. All patients with total ventilator days at least 28 days and all PICU nonsurvivors were assigned VFD = 0.

TABLE 5. Predictive Validity of 24-Hour Oxygenation Index and Worst Oxygenation Index in the First 24 Hours

	24-hr OI[a]				Worst OI in 24 hr[b]			
Variable	< 4	4 to < 8	8 to < 16	≥ 16	< 4	4 to < 8	8 to < 16	≥ 16
Number of patients	25	137	83	32	1	64	117	101
Mortality (%) (95% CI)	0 (0) (0–9)	13 (9) (5–15)	13 (16) (9–25)	9 (28) (15–45)	0 (0)	3 (5) (1–12)	12 (10) (6–17)	22 (22) (15–31)
VFD 0 at 28 d (%) (95% CI)	0 (0) (0–9)	22 (16) (11–23)	25 (30) (21–41)	14 (44) (28–61)	0 (0)	7 (11) (5–20)	22 (19) (13–27)	35 (35) (26–44)
VFD ≤ 14 d (%) (95% CI)	3 (12) (3–29)	41 (30) (23–38)	47 (57) (46–67)	20 (63) (45–78)	0 (0)	18 (28) (18–40)	44 (38) (29–47)	53 (52) (43–62)
VFDs, median (IQR)	22 (17, 23)	19 (11, 22)	10 (0, 18)	9 (0, 18)	17	19 (13, 23)	18 (8, 21)	13 (0, 19)
Ventilator days in survivors, median (IQR)	6 (5, 11)	8 (6, 13)	14 (9, 23)	14 (10, 26)	11	9 (5, 14)	9 (7, 17)	11 (8, 22)

OI = oxygenation index, VFD = ventilator-free days, IQR = interquartile range.

[a]Comparisons of mortality, VFD = 0 at 28 d, VFD ≤ 14 d, VFDs, and ventilator days in survivors across Pediatric Acute Lung Injury Consensus Conference (PALICC) categories using 24-hr OI were all statistically significant ($p < 0.001$).

[b]Comparisons of mortality ($p = 0.001$), VFD = 0 at 28 d ($p < 0.001$), VFD ≤ 14 d ($p = 0.001$), and VFDs ($p < 0.001$) across PALICC categories using the worst OI in the first 24 hr were all statistically significant. Comparison of ventilator days in survivors ($p = 0.075$) did not reach statistical significance.

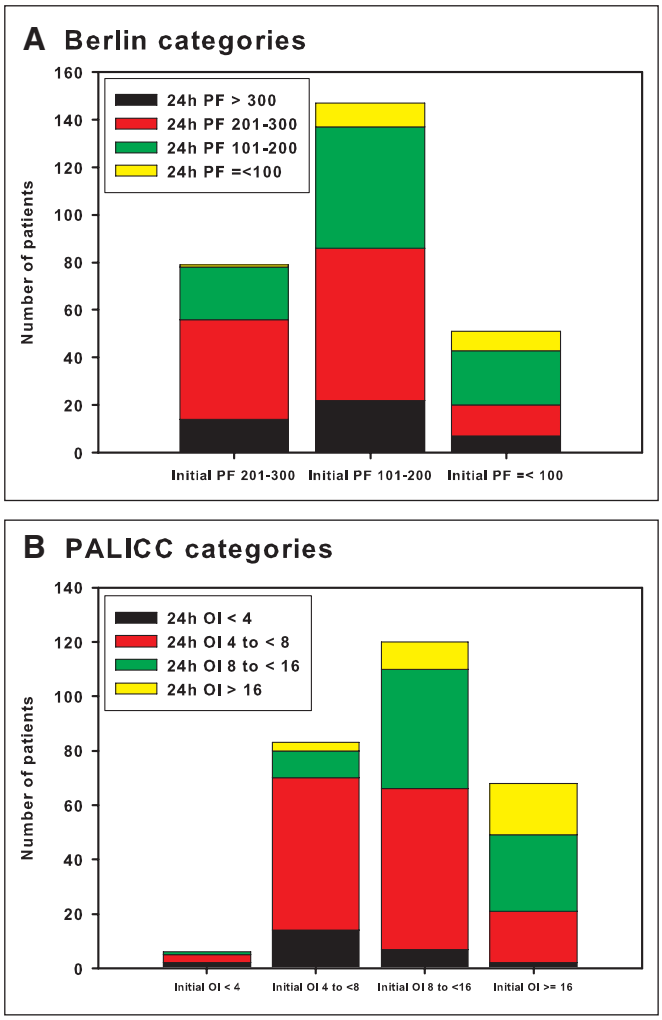

Figure 3. Reclassification of patients based on their initial and 24-hr Berlin (**A**) or Pediatric Acute Lung Injury Consensus Conference (PALICC) (**B**) oxygenation categories. OI = oxygenation index, PF = Pao_2/Fio_2.

Statistical Analysis

Data are expressed as percentages or as median (interquartile range, IQR). All variables were found to be nonnormally distributed by Shapiro-Wilk. Differences between distributions of categorical variables were analyzed by Fisher exact test. Continuous variables were compared using Kruskal-Wallis test. The 95% CI for categorical variables were computed using Jeffreys interval for binomial proportion. In some analyses, the outcome VFDs at 28 days was dichotomized to days 0 or more than 0 days or separately as up to 14 days or more than 14 days. A nonparametric test of trend was used to test if rates of mortality, VFDs = 0, or VFD up to 14 increased across worsening ARDS severity. Receiver operating characteristic curves were constructed for testing predictive ability of the Berlin and PALICC definitions of ARDS using dummy variables for oxygenation categories. Data were analyzed using Stata 10.0 (StataCorp, LP, College Station, TX).

RESULTS

Characteristics of the ARDS Cohort

During the study period, 10,618 patients were admitted to the CHOP PICU, of whom 2,851 were anticipated to be ventilated more than 24 hours. Of these 2,851, the 737 patients with arterial catheters underwent screening, and 283 met eligibility criteria (**Fig. 1**). This gave an ARDS prevalence of 2.7% of PICU admissions and 9.9% of those ventilated more than 24 hours. Characteristics of the ARDS cohort are summarized in **Table 1**. Chronic comorbidities were present in 168 patients (59%). Pneumonia (58%) and sepsis (18%) accounted for most lung injury. Median Pao_2/Fio_2 at ARDS onset was 156 (IQR, 110, 205), with an OI of 10.2 (IQR, 7.1, 16.3), derived from all 283 patients. At ARDS onset, 266 children were ventilated with conventional ventilation, six children with high-frequency percussive ventilation (HFPV), and 11 children with high-frequency oscillatory ventilation (HFOV). The 266 patients on conventional ventilation received a median PEEP of 10 cm H_2O (IQR, 8, 12; range, 5–16) and an exhaled tidal volume (V_T) of 7.5 mL/kg actual body weight (IQR, 6.7, 8.3).

Twenty-four hours after meeting ARDS criteria, 61 patients transitioned to alternative modes (33 HFPV, 24 HFOV, and four airway pressure release ventilation, APRV), five patients escalated to ECMO (three venovenous and two venoarterial), and one patient died. In the 277 surviving patients not on ECMO in whom Pao_2/Fio_2 and OI could be computed, Pao_2/Fio_2 had improved to 222 (IQR, 165, 274) and OI to 6.9 (5.2, 10.5). At 24 hours, in the 216 patients remaining on conventional ventilation, PEEP and V_T were not substantially different than at ARDS onset (PEEP range, 5–15 cm H_2O).

In total, 99 patients transitioned to HFPV ($n = 48$), HFOV ($n = 36$), or APRV ($n = 15$) within 72 hours of ARDS, of whom 14 died. Thirteen patients transitioned to ECMO at any point (seven venovenous and six venoarterial), with three deaths (all venoarterial). There were 37 total PICU deaths (eight persistent hypoxemia, 11 multisystem organ failure, and 18 withdrawal of care), for an overall mortality rate of 13%.

Predictive Ability of Oxygenation Metrics

Initial Berlin Pao_2/Fio_2 and PALICC OI categories at ARDS onset failed to discriminate mortality; however, values 24 hours afterward, as well as the worst values in 24 hours, discriminated mortality (**Table 2**). Similar results were obtained for VFD = 0 days or VFD up to 14 days (**Table 3**). Berlin categories using initial Pao_2/Fio_2 values did not demonstrate differing mortality between mild and moderate but showed elevation in the severe category (**Fig. 2A**). However, the Pao_2/Fio_2 24 hours afterward, and the worst Pao_2/Fio_2 in the first 24 hours, demonstrated stepwise increase in mortality across worsening categories (**Fig. 2, B** and **C**). Similar results were seen for PALICC categories (**Fig. 2 D–F**), except for a small number of patients ($n = 6$) with OI less than 4 despite a qualifying Pao_2/Fio_2 up to 300 (Fig. 2*D*).

Under Berlin oxygenation categories, 33 patients were reclassified to a more severe Pao_2/Fio_2 category at 24 hours and 143 patients to a less severe category. Similarly, using PALICC

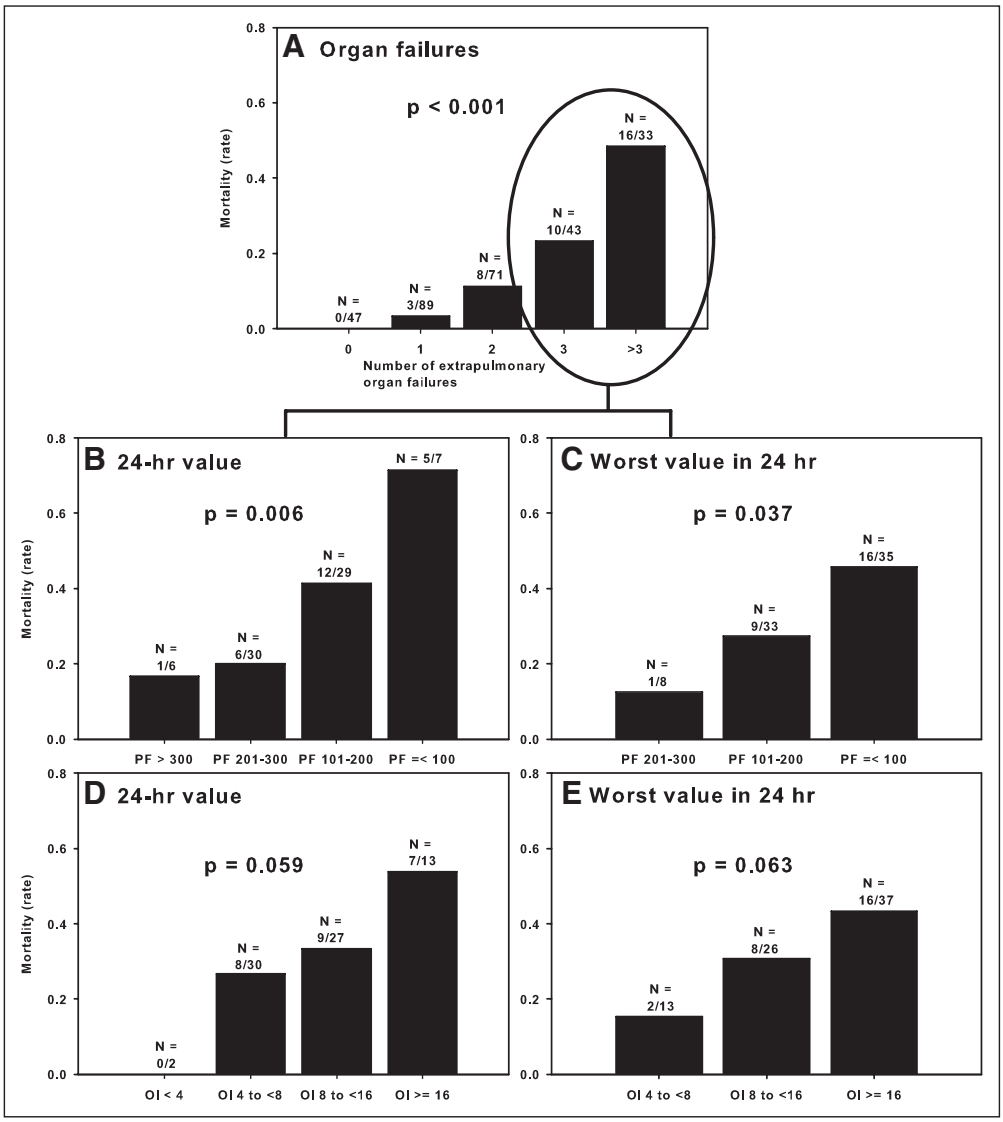

Figure 4. Mortality in relation to extrapulmonary organ failure (**A**) and classification based on Berlin (**B** and **C**) and Pediatric Acute Lung Injury Consensus Conference (**D** and **E**) oxygenation categories based on 24-hr or worst value of Pao_2/Fio_2 (PF) or oxygenation index (OI). B–E, Mortality stratification in patients at highest risk of death (≥ 3 extrapulmonary organ failures at acute respiratory distress syndrome diagnosis). *p* values represent a nonparametric test for trend, testing if mortality increases across increasing number of failing organs (A) or worsening oxygenation categories (B–E).

categories, 27 patients were reclassified to higher severity categories based on 24-hour OI and 129 patients to a less severe category (**Fig. 3**).

Berlin and PALICC categories derived from the Pao_2/Fio_2 (**Table 4**) and OI (**Table 5**) 24 hours after ARDS onset demonstrated fewer VFD and increased duration of ventilation in survivors across worsening categories (all $p < 0.001$ for differences in VFD or duration of ventilation). Corresponding categories derived from the worst Pao_2/Fio_2 or OI, however, did not demonstrate fewer VFDs or increasing duration of ventilation; however, both worst and 24-hour values adequately discriminated the dichotomous outcomes of mortality, VFD = 0 days, and VFD up to 14 days.

Oxygenation categories derived from 24 hours and worst Pao_2/Fio_2 and OI performed well in high-risk cohorts with higher mortality, suggesting durability of these metrics independent of mortality risk. Increasing extrapulmonary organ failures at ARDS diagnosis correlated with increasing mortality rate (**Fig. 4**). In subgroups with the highest mortality (≥ 3 organ failures, 34% mortality), the 24-hour and worst values adequately discriminated mortality (Fig. 4). Similar results were found for immunocompromised patients (35% mortality) (**Fig. 5**)

Because iNO may temporarily improve oxygenation, the impact of this therapy was studied. We conducted a parallel analysis excluding patients exposed to iNO (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B189; **Supplementary Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/B190; and **Supplementary Table 3**, Supplemental Digital Content 3, http://links.lww.com/CCM/B191). In this subgroup, we reconfirmed that initial Pao_2/Fio_2 and OI did not discriminate mortality and redemonstrated that 24-hour Pao_2/Fio_2 and OI retained predictive ability for mortality, VFDs, and duration of ventilation in survivors. In this smaller cohort, worst Pao_2/Fio_2 and OI were unable to discriminate mortality, VFD = 0 days, or VFD up to 14 days.

DISCUSSION

We report the largest PARDS cohort undergoing invasive ventilation described to date in North America, the most recent testing Berlin criteria in children, and the first external validation of PALICC categories. Berlin categories based on initial Pao_2/Fio_2 did not discriminate outcomes. However, classification based on either the 24-hour Pao_2/Fio_2 or the worst Pao_2/Fio_2 in the first 24 hours better discriminated the outcomes of mortality, VFD = 0 at 28 days, or VFD up to 14 days. The 24-hour Pao_2/Fio_2 best categorized degree of lung injury, as demonstrated by stepwise fewer VFDs and longer duration of

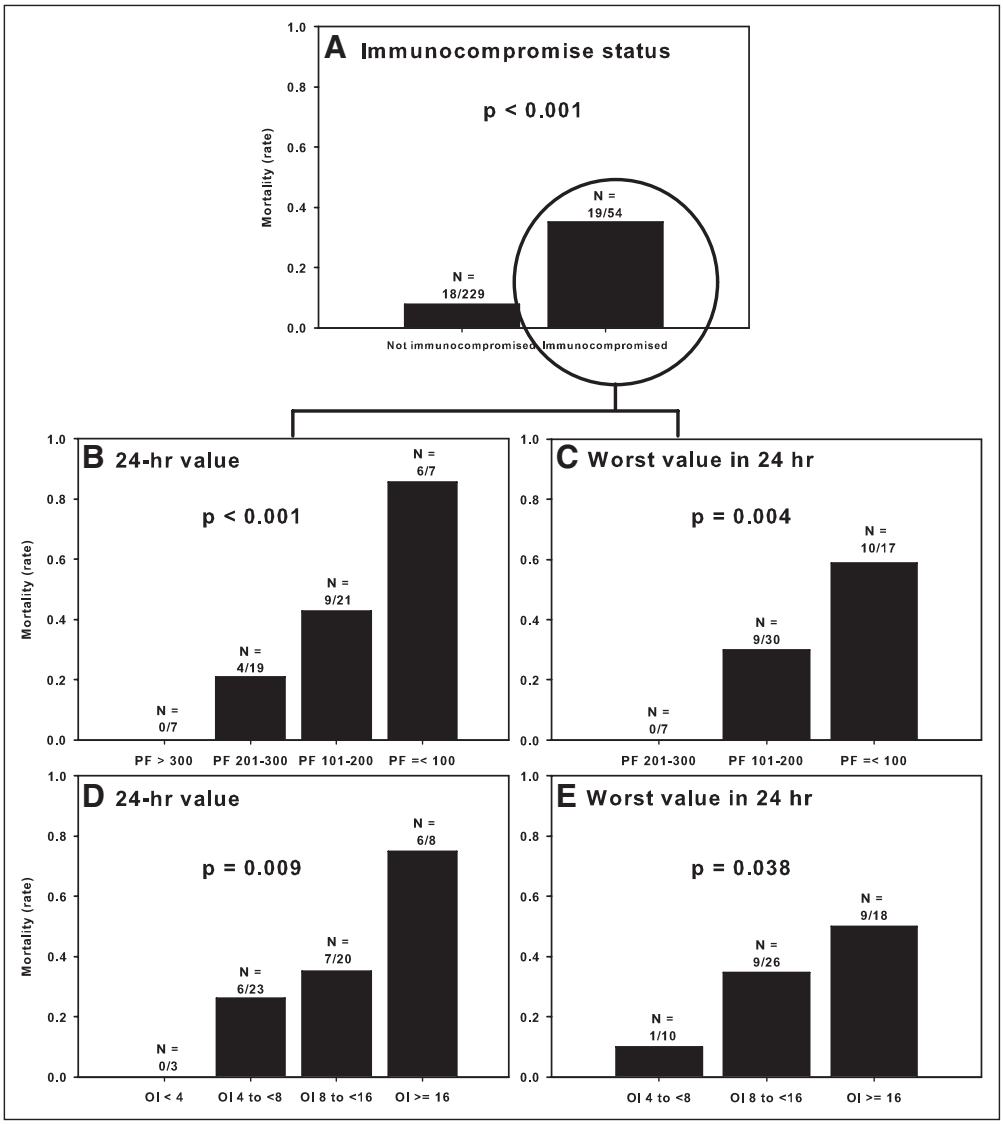

Figure 5. Mortality in relation to immunocompromised status (**A**) and classification based on Berlin (**B** and **C**) and Pediatric Acute Lung Injury Consensus Conference (**D** and **E**) oxygenation categories based on 24-hr or worst value of Pao_2/Fio_2 (PF) or oxygenation index (OI). *p* Values represent Fisher exact test (A) or nonparametric tests for trend (B–E) testing if mortality increases across worsening oxygenation categories.

mechanical ventilation in survivors. Similar results were seen for PALICC categories based on OI.

Our ARDS prevalence (5, 6, 20, 21) and severity of illness (4, 6, 22, 23) were similar to prior cohorts, with comparable PRISM III (4, 6) and initial Pao_2/Fio_2 at ARDS diagnosis (4, 23). Our initial PEEP of 10 cm H_2O (IQR, 8, 12) is double that reported by Flori et al (4) and Hu et al (20) and more consistent with Pediatric Acute Lung Injury Epidemiology and Natural History (6) and the Australian/New Zealand cohorts (5), possibly suggesting increasing comfort with higher PEEP in pediatrics. Similarly, our use of nonconventional ventilator modes (6% at diagnosis of ARDS, 35% within 72 hr) is consistent with recent reports (5, 6) but is higher than reported in older studies (3, 4). The 13% mortality is lower than reported by most observational studies (4–6, 20, 24, 25) but consistent with contemporary cohorts (**Fig. 6**) (22, 23) and some randomized trials (26–28). This may reflect improving care over time or adoption of adult-based evidence, including lower V_T (29), higher PEEP (30, 31), or fluid restriction (32).

De Luca et al (22) recently performed validation of Berlin criteria in infants and demonstrated that improved performance of the Berlin definition was due to introduction of a "severe" category with higher mortality, with little difference seen between mild and moderate. These results parallel our data (Fig. 2), as De Luca et al (22) extracted initial Pao_2/Fio_2 at time of ARDS diagnosis.

Although others have demonstrated that persistence of oxygenation defect is associated with mortality (6, 21, 33), we are the first to test this using Berlin and PALICC categories in children and to accurately categorize lung injury using 24-hour Pao_2/Fio_2 and OI. Oxygenation measurements at ARDS onset may poorly predict outcome because of inadequate lung recruitment and underresuscitation affecting Pao_2; the same measurements after 24 hours of attempted stabilization may more accurately reflect lung injury. Ventilation/perfusion mismatches present at ARDS onset may be improved after 24 hours, thus allowing oxygenation metrics to more accurately reflect true shunt. This is supported by our finding that four times as many patients were reclassified to a less severe category at 24 hours than to a more severe one (Fig. 3). Villar et al (11, 12) suggested measuring Pao_2/Fio_2 on standard ventilator settings (PEEP ≥ 10 cm H_2O, $Fio_2 \geq 0.5$) 24 hours after ARDS for stratifying outcomes in adults. We report compatible results, with an important difference being absence of standardized ventilator settings. Of 277 evaluable Pao_2/Fio_2 and OI at 24 hours of ARDS, 61 were calculated while on HFPV, HFOV, or APRV, with the remaining 216 patients having a median PEEP 10 cm H_2O (IQR, 8, 10) ; the median Fio_2 for all 277 was 0.40 (IQR, 0.35, 0.50). These settings are remarkably close to those advocated by Villar et al (11, 12). Our results confirm the limited utility of initial Pao_2/Fio_2 relative to the 24-hour values; whether this can be further

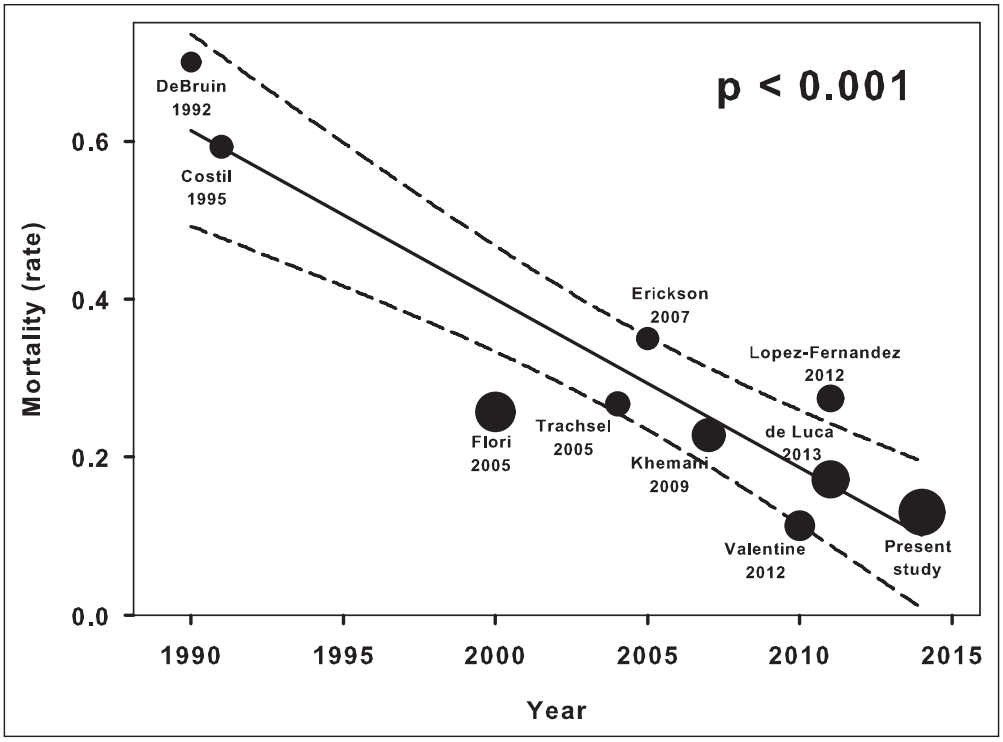

Figure 6. Mortality rates over time in published pediatric observational cohorts in the Western hemisphere with sample sizes at least 100 ventilated patients with diverse acute lung injury/acute respiratory distress syndrome-type entry criteria. The *solid regression line* shows a decreasing mortality over time, with *dotted lines* depicting 95% CIs. Size of *circles* reflects relative sample sizes. The assigned year represents the final year of patient accrual for a given study. Since we wished to compare the mortalities of as homogenous a population as possible, Flori et al (4) were restricted to the 237 initially intubated patients, and Khemani et al (21) restricted to the 192 patients with bilateral infiltrates on radiograph.

improved by standardized settings in children requires further validation.

Berlin and PALICC categories derived from the 24-hour Pao_2/Fio_2 and OI better categorized lung injury, as demonstrated by fewer VFDs and longer duration of ventilation in survivors (Tables 4 and 5). One cost of this improved characterization is a drop in sample size: while 56 patients met Berlin criteria for severe ARDS based on initial Pao_2/Fio_2, by 24 hours this category only contained 19 patients. In pediatrics, this may potentially be addressed by substituting mortality with alternative outcomes (VFD = 0 at 28 d or VFD ≤ 14) which occur more frequently than death. Needing to wait 24 hours to categorize ARDS severity should not impact recruitment, as most published trials enrolled up to 48 hours after meeting ARDS criteria (26, 27, 34). Indeed, the Prone Positioning for Severe ARDS trial (35) restricted entry criteria to Pao_2/Fio_2 up to 150, which was reconfirmed 12–24 hours after initially meeting entry criteria, suggesting that persistently poor Pao_2/Fio_2 can be used as entry criteria to accurately identify more severely affected subgroups in which to test interventions.

Our study has limitations that may affect comparisons and generalizability. The study was conducted at a single center, and although demographics and severity of illness are comparable to other PARDS cohorts, mortality rate, ventilator practices, and utilization of ancillary therapies or alternative ventilator modes may not allow translation to other PICUs. Also, as we restricted enrollment to patients undergoing invasive ventilation with arterial access and required two consecutive Pao_2/Fio_2 up to 300, we selected only a fraction of patients with respiratory failure. However, our eligibility criteria were similar to many PARDS trials (27, 34). Exclusion of patients without arterial access likely resulted in an underestimation of ARDS prevalence (36); however, as the Berlin definition requires invasive Pao_2/Fio_2, for this definition, at least we provide a reasonable estimate. Finally, as the study was initiated in 2011 before publication of either the Berlin or PALICC definitions, we were limited by our inclusion criteria of 1) invasive mechanical ventilation, 2) Pao_2/Fio_2 up to 300, and 3) bilateral infiltrates. Although this allowed universal application of the Berlin criteria to our population, it limited true validation of the predictive ability of the PALICC criteria: we could only judge utility of the PALICC criteria in patients who already met Berlin criteria. Despite this limitation, we demonstrated that OI 24 hours after meeting PARDS criteria had better predictive ability for outcome and more accurately categorized severity of lung injury.

CONCLUSIONS

Pao_2/Fio_2 and OI measured 24 hours after ARDS onset accurately stratified outcomes in this PARDS cohort, although initial values were not helpful for prognostication. Definitions of ARDS may benefit from addressing timing of oxygenation metrics to stratify disease severity.

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