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Epidemiology and Outcomes of Critically Ill Children at Risk for Pediatric Acute Respiratory Distress Syndrome: A Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology Study

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OBJECTIVES: Interventional trials aimed at pediatric acute respiratory distress syndrome prevention require accurate identification of high-risk patients. In this study, we aimed to characterize the frequency and outcomes of children meeting "at risk for pediatric acute respiratory distress syndrome" criteria as defined by the Pediatric Acute Lung Injury Consensus Conference.

DESIGN: Planned substudy of the prospective multicenter, international Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology study conducted during 10 nonconsecutive weeks (May 2016–June 2017).

SETTING: Thirty-seven international PICUs.

PATIENTS: Three-hundred ten critically ill children meeting Pediatric Acute Lung Injury Consensus Conference "at-risk for pediatric acute respiratory distress syndrome" criteria.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We evaluated the frequency of children at risk for pediatric acute respiratory distress syndrome and rate of subsequent pediatric acute respiratory distress syndrome diagnosis and used multivariable logistic regression to identify factors associated with subsequent pediatric acute respiratory distress syndrome. Frequency of at risk for pediatric acute respiratory distress syndrome was 3.8% (95% CI, 3.4–5.2%) among the 8,122 critically ill children who were screened and 5.8% (95% CI, 5.2–6.4%) among the 5,334 screened children on positive pressure ventilation or high-flow oxygen. Among the 310 at-risk children, median age was 2.1 years (interquartile range, 0.5–7.3 yr). Sixty-six children (21.3%) were subsequently diagnosed with pediatric acute respiratory distress syndrome, a median of 22.6 hours (interquartile range, 9.8–41.0 hr) later. Subsequent pediatric acute respiratory distress syndrome was associated with increased mortality (21.2% vs 3.3%; $p < 0.001$) and longer durations of invasive ventilation and PICU care. Subsequent pediatric acute respiratory distress syndrome rate did not differ by respiratory support modality at the time of meeting at risk criteria but was independently associated with lower initial saturation:F_{IO_2} ratio, progressive tachycardia, and early diuretic administration.

CONCLUSIONS: The Pediatric Acute Lung Injury Consensus Conference "at-risk for pediatric acute respiratory distress syndrome" criteria identify critically ill children at high risk of pediatric acute respiratory distress syndrome and poor outcomes. Interventional trials aimed at pediatric acute respiratory distress syndrome prevention should target patients early in their illness course and include patients on high-flow oxygen and positive pressure ventilation.

KEY WORDS: acute respiratory distress syndrome; mechanical ventilation; pediatric; respiratory failure

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Pediatric acute respiratory distress syndrome (PARDS) occurs in 2–4% of patients admitted to PICUs, has a contemporary mortality rate of 20%, and has no specific treatment (1–3). Identifying children at risk for developing PARDS could lead to targeted therapies to prevent disease progression and improve outcomes. Trials to identify such disease-modifying therapies in adults were enabled after the Lung Injury Prediction Score was validated to identify at-risk patients and, more recently, the Prevention and Early Treatment of Acute Lung injury (PETAL) network was funded to study these interventions (4–10).

Criteria to identify children At Risk For PARDS (ARF-PARDS) were established by the Pediatric Acute Lung Injury Consensus Conference (PALICC) in 2015 and differ from PARDS criteria only in regards to the oxygenation criterion (**Supplemental Fig. 1**, http://links.lww.com/CCM/G779; **legend**, http://links.lww.com/CCM/G790) (2). Children on invasive mechanical ventilation (MV) or full-face noninvasive ventilation (NIV) are diagnosed with ARF-PARDS instead of PARDS when hypoxemia is mild (e.g., oxygenation index < 4). Children on nasal modes of respiratory support (e.g., high-flow nasal cannula) are ineligible for PARDS because the possible entrainment of room air makes hypoxemia measures unreliable but are diagnosed with ARF-PARDS when the other criteria are met (2). Currently, the prevalence, natural history, and outcomes of children meeting ARF-PARDS criteria are unknown.

The PARDS Incidence and Epidemiology (PARDIE) study recently screened all PICU patients in 145 centers across five continents to describe the epidemiology and outcomes of PARDS and ARF-PARDS (1). In order to provide a better understanding of the feasibility of clinical trials targeting PARDS prevention, the aim of this planned ARF-PARDS substudy was to describe the epidemiology and outcomes of children meeting ARF-PARDS criteria, including the frequency, timing, and risk factors of a subsequent diagnosis of PARDS.

METHODS

The main PARDIE study prospectively screened children admitted to 145 participating PICUs in 27 countries during 10 nonconsecutive weeks between May 2016 and June 2017 and enrolled all children newly meeting PALICC PARDS criteria (1, 2). Thirty-seven sites decided a priori to participate in this additional ARF-PARDS substudy with approval from each site's Institutional Review Board.

Creation of ARF-PARDS Substudy Cohort

Each study week, participating centers (**Appendix 1**) screened all children treated in the PICU for five consecutive days. Patients were eligible for inclusion in this ARF-PARDS substudy if they met PALICC criteria for ARF-PARDS for the first time in the preceding 24 hours (2). The ARF-PARDS criteria are a risk factor ("trigger") for PARDS within the preceding 7 days, acute pulmonary parenchymal disease on chest radiograph, and hypoxemia thresholds related to respiratory support modality and age. Children with respiratory disease explained by cardiac failure or fluid overload, convalescing from a cardiac intervention, or with active perinatal lung disease are ineligible for ARF-PARDS, and thus were excluded from this study. Data collected for each eligible subject included demographics, geographic region, PARDS trigger, comorbidities, respiratory support modalities, subsequent diagnosis of PARDS, and clinical outcomes. In addition, selected treatments and serial vital signs (every 6 hr) were collected for the first 3 days after ARF-PARDS diagnosis or until death, PICU discharge, or PARDS diagnosis.

Variable Definitions

Respiratory support modalities were collected as invasive MV, full-face NIV, nasal NIV, and high-flow oxygen (HFO) via mask or nasal cannula. Vital signs were defined as "initial" (collected within 2 hr of ARF-PARDS diagnosis) and "next" (collected 1–12 hr after the initial value), with the "change" equal to the next value minus the initial value. The ratio of measured oxygen saturation (Spo_2) to Fio_2 (SF ratio) was calculated as previously described when Spo_2 was less than 98% (11). The prescribed oxygen fraction was used as Fio_2 regardless of support mode.

Outcomes and Main Analyses

The frequency of ARF-PARDS is presented with descriptive statistics and compared between geographic regions using chi-square tests. The primary outcome of the study was a subsequent diagnosis of PARDS, which was compared between geographic regions and between respiratory support modalities using chi-square

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tests. Secondary outcomes were PICU mortality, 28-day PICU-free days (PFDs), and 28-day ventilator-free days (VFDs). PFDs and VFDs were calculated by subtracting PICU length of stay or duration of invasive MV, respectively, from 28. Children who died before PICU discharge were assigned zero PFDs and zero VFDs. Secondary outcomes were compared between subjects with and without subsequent PARDS using chi-square (mortality) and Wilcoxon rank-sum (PFDs and VFDs). A multivariate model of time to PICU discharge with death as a competing risk (as a way to model PFDs) was built to determine if subsequent PARDS was independently associated with fewer PFDs. Demographic and physiologic variables available from the time of ARF-PARDS diagnosis were used to predict PFDs using forward stepwise selection to identify variables with a univariable p value of less than 0.05, and all variables that remained statistically significant or significantly improved model fit per the likelihood-ratio test were retained. Then, we added "subsequent PARDS" to the model to evaluate if the subsequent diagnosis of PARDS was independently associated with fewer PFDs after controlling for the competing risk of death (where a subdistribution hazard ratio [sdHR] < 1 indicates longer time to PICU discharge).

Analyses to Identify Factors Associated With Subsequent PARDS

First, univariate analyses were performed with chi-square or Fisher exact tests (categorical variables) and Wilcoxon rank-sum test (continuous variables) to preliminarily identify factors associated with a subsequent diagnosis of PARDS. This included testing for associations between medications administered on the day of ARF-PARDS diagnosis ("day 0") with a PARDS diagnosis on day 1 or later. Then, we constructed a hierarchical, multivariable logistic regression model to identify factors associated with subsequent PARDS, controlling for center as a random effect. A priori, we planned to evaluate all factors associated ($p < 0.10$) with subsequent PARDS in univariate analysis for inclusion in the model, followed by individually testing the following variables preselected based on biologic plausibility: age, comorbidities, PARDS trigger, respiratory support modality at ARF-PARDS diagnosis, bilateral infiltrates on chest radiograph, and home respiratory support modality. Variables with a p value of less than 0.05 or that changed other variable effect estimates by greater than 20% were retained in the final model. Initial and next vital signs were both assessed for inclusion in the model rather than the change in vital sign (12); if a next vital sign met criteria to be retained, its initial value was also included. Subjects missing retained variables were excluded from the model.

Subgroup Analyses

The subjects were divided into two mutually exclusive subgroups based on use of nonnasal (invasive MV or full-face NIV) or nasal (nasal NIV or HFO) respiratory support at the time of ARF-PARDS diagnosis and the above analyses repeated. In each subgroup, univariate analyses were used to identify factors associated with subsequent PARDS. Then, a model was constructed as described above for each subgroup to identify factors associated with subsequent PARDS.

Analyses were performed using SigmaPlot v12.5 (Systat Software, San Jose, CA) or SAS v9.4 (SAS Institute, Cary, NC). Data are shown as median (interquartile range [IQR]), 95% CIs are reported where appropriate, and p value of less than 0.05 defined statistical significance. Model results are shown as adjusted odds ratios with 95% CIs.

RESULTS

Epidemiology and Outcomes of ARF-PARDS

Thirty-seven centers in thirteen countries participated in the ARF-PARDS substudy. During the study period, 8,122 children were screened for inclusion, 5,334 of whom were supported by invasive MV, NIV, or HFO. The criteria for ARF-PARDS were met in 310 children, giving a frequency of 3.8% (95% CI, 3.4–5.2%) among all PICU patients and 5.8% (5.2–6.4%) among those on invasive MV, NIV, or HFO. The prevalence of ARF-PARDS differed significantly across geographic regions (**Fig. 1**) with North American centers (n = 260 children) having the highest prevalence of ARF-PARDS (4.4% of all patients; 6.7% of patients receiving invasive MV, NIV, or HFO).

Among the 310 subjects who met ARF-PARDS criteria, the median age was 2.1 years (IQR, 0.5–7.3 yr), 63.5% had a comorbidity, and 73.9% had an acute lower respiratory tract infection (**Table 1**). ARF-PARDS criteria were met within 1 hour of PICU admission in 127 (41.0%) children, including 57 (18.4%)

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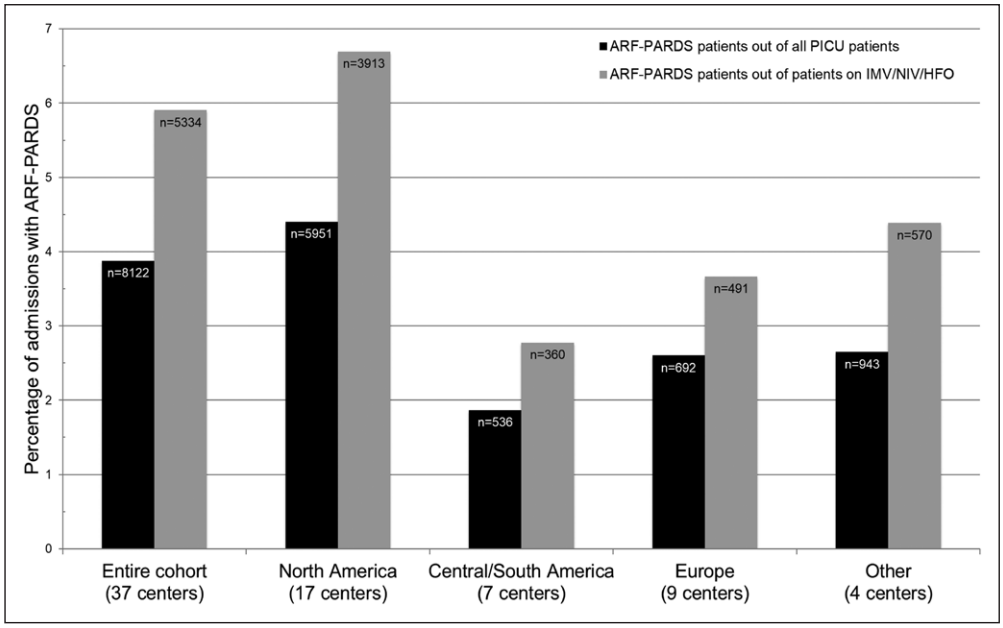

Figure 1. At Risk For Pediatric Acute Respiratory Distress Syndrome (ARF-PARDS) prevalence by region. The *black bar* shows the percentage of all screened patients who met ARF-PARDS criteria for each region, with the number of screened patients reported within the *bar*. The *gray bar* shows the percentage of patients who met ARF-PARDS criteria for each region relative to the number of patients who were on invasive mechanical ventilation (IMV), noninvasive ventilation (NIV), or high-flow oxygen (HFO) at the time of screening, with the number of screened patients on invasive MV, NIV, or HFO reported within the *bar*. The percentage of admissions meeting ARF-PARDS criteria differed significantly between the four regions for both all screened patients and all patients on respiratory support (both $p < 0.01$ by χ^2 test).

who met the criteria before PICU admission. At the time of ARF-PARDS diagnosis, 71.6% were on a nasal mode (including 58.4% on HFO) and 28.4% on a nonnasal mode (including 24.2% on invasive MV). After ARF-PARDS diagnosis, beta-agonist medications were used in 56.5% of subjects and corticosteroids in 44.2% (**Supplemental Table 1**, http://links.lww.com/CCM/G780). Diuretics (33.5%), blood products (10.3%), and parenteral nutrition (5.8%) were also used. Twenty-two children died (7.1%) before PICU discharge and the median PFDs was 22.2 (14.0–25.1).

Epidemiology and Outcomes of Subsequent PARDS

Among all subjects, PARDS was subsequently diagnosed in 66 children (21.3% [95% CI, 16.7–25.8%]). The rate of PARDS differed significantly between regions (**Supplemental Fig. 2**, http://links.lww.com/CCM/G781; legend, http://links.lww.com/CCM/G790), but not by respiratory support modality at ARF-PARDS diagnosis (invasive MV: 20.0%, full-face NIV: 30.7%, nasal NIV: 17.1%, HFO: 22.1%; $p = 0.74$). Among those subsequently diagnosed with PARDS, the median interval between ARF-PARDS diagnosis and PARDS diagnosis was 22.6 hours (9.8–41.0 hr) (**Fig. 2**). The median interval between PARDS trigger and PARDS diagnosis was 35.3 hours (22.5–61.6 hr). Children with ARF-PARDS who were subsequently diagnosed with PARDS had higher ICU mortality (21.2% vs 3.3%), fewer PFDs (12.0 [0.0–19.3] vs 23.4 [19.1–25.5]), and fewer VFDs (17.8 [0.0–24.5] vs 28.0 [26.8–28.0]) than children never diagnosed with PARDS (all $p < 0.01$). In the multivariate model, subsequent PARDS (sdHR, 0.27; 95% CI, 0.19–0.38) was independently associated with fewer PFDs after controlling for comorbidity, PARDS trigger, initial SF ratio, and initial mode of ventilation (**Supplemental Table 2**, http://links.lww.com/CCM/G782).

Risk Factors for Subsequent PARDS

Among all subjects, initial Fio_2 and SF ratio, and later measures of heart rate, Spo_2, Fio_2, and SF ratio were associated with subsequent PARDS (**Table 2**). Children diagnosed with PARDS after day 0 of ARF-PARDS diagnosis were more likely to receive blood products, diuretics, and parenteral nutrition on day 0 than children never diagnosed with PARDS (**Supplemental Table 3**, http://links.lww.com/CCM/G783). In the multivariate model ($n = 204$), lower initial SF ratio, higher next heart rate, and diuretic administration on day 0 were significantly associated with increased odds of subsequent PARDS (**Table 3**). Findings were similar when heart rate was removed in order to increase the number of children in the model ($n = 269$).

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TABLE 1.
Patient Characteristics Associated With a Subsequent Diagnosis of Pediatric Acute Respiratory Distress Syndrome Among All Subjects

Characteristic	Entire Cohort (*n* = 310)	Subsequent PARDS (*n* = 66)	No Subsequent PARDS (*n* = 244)	*p*
Age, yr, median (IQR)	2.1 (0.5–7.3)	2.6 (0.8–8.5)	2.0 (0.5–6.7)	0.21
Weight, kg, median (IQR)	11.7 (7.4–24.0)	13.5 (7.2–28.4)	11.2 (7.4–22.2)	0.26
Female, *n* (%)	136 (43.9)	30 (45.5)	106 (43.4)	0.77
Race–Asian/American Indian/Pacific Islander, *n* (%)	18 (5.8)	6 (9.1)	12 (4.9)	0.37
Black	43 (13.9)	6 (9.1)	37 (15.2)	
White	188 (60.7)	42 (63.6)	146 (59.8)	
Other/unknown/multiracial	61 (19.7)	12 (18.2)	49 (20.1)	
Hispanic, *n* (%)	56 (18.1)	16 (24.2)	40 (16.4)	0.14
Days from PICU admission to ARF-PARDS	0.1 (0.0–0.6)	0.1 (0.0–0.9)	0.1 (0.0–0.6)	0.43
Risk factor–aspiration, *n* (%)	22 (7.1)	6 (9.1)	16 (6.6)	0.41
Bacterial LRTI	56 (18.1)	14 (21.2)	42 (17.2)	
Viral LRTI	124 (40.0)	21 (31.8)	103 (42.2)	
Other LRTI	49 (15.8)	10 (15.2)	39 (15.98)	
Sepsis	22 (7.1)	8 (12.1)	14 (5.7)	
Trauma	16 (5.2)	4 (6.1)	12 (4.9)	
Other	21 (6.8)	3 (4.6)	18 (7.4)	
Admission source–internal/external floor, *n* (%)	122 (39.4)	28 (42.4)	94 (38.5)	0.16
Internal/external emergency department	145 (46.8)	25 (37.9)	120 (49.2)	
Other	43 (13.9)	13 (19.7)	30 (12.3)	
Support at ARF-PARDS–high-flow oxygen, *n* (%)	181 (58.4)	40 (60.6)	141 (57.8)	0.92
Noninvasive ventilation	54 (17.4)	11 (16.7)	43 (17.6)	
Invasive mechanical ventilation	75 (24.2)	15 (22.7)	60 (24.6)	
Bilateral infiltrates on chest radiograph, *n* (%)	203 (65.5)	49 (74.2)	154 (63.1)	0.09
Any comorbidity, *n* (%)	197 (63.6)	43 (65.2)	154 (63.1)	0.76
Asthma	46 (14.8)	6 (9.1)	40 (16.4)	0.14
Cardiac acquired	13 (4.2)	3 (4.6)	10 (4.1)	> 0.99
Cardiac congenital	37 (11.9)	8 (12.1)	29 (11.9)	0.96
Neuromuscular disease	59 (19.0)	9 (13.6)	50 (20.5)	0.21
Oncologic/immunologic	29 (9.4)	8 (12.1)	21 (8.6)	0.38
Prematurity	68 (21.9)	15 (22.7)	53 (21.7)	0.86
Pulmonary (nonasthma)	59 (19.0)	16 (24.2)	43 (17.6)	0.22
Home respiratory support–none, *n* (%)	253 (81.6)	54 (81.8)	199 (81.6)	0.69
Noninvasive ventilation	17 (5.5)	4 (6.1)	13 (5.3)	
Oxygen	16 (5.2)	5 (7.6)	11 (4.5)	
Tracheostomy without ventilator	12 (3.9)	2 (3.0)	10 (4.1)	
Tracheostomy with ventilator	12 (3.9)	1 (1.5)	11 (4.5)	

(*Continued*)

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TABLE 1. (*Continued*).

Patient Characteristics Associated With a Subsequent Diagnosis of Pediatric Acute Respiratory Distress Syndrome Among All Subjects

Characteristic	Entire Cohort ($n = 310$)	Subsequent PARDS ($n = 66$)	No Subsequent PARDS ($n = 244$)	*p*
ICU mortality, *n* (%)	22 (7.1)	14 (21.2)	8 (3.3)	< 0.01
PICU-free days, median (IQR)	22.2 (14.0–25.1)	12.0 (0.0–19.3)	23.4 (19.1–25.5)	< 0.01
Ventilator-free days, median (IQR)	28.0 (23.7–28.0)	17.8 (0.0–24.5)	28.0 (26.8–28.0)	< 0.01

ARF-PARDS = At Risk For Pediatric Acute Respiratory Distress Syndrome, IQR = interquartile range, LRTI = lower respiratory tract infection, PARDS = pediatric acute respiratory distress syndrome.

Data missing in age ($n = 8$), weight ($n = 1$), and ventilator-free day ($n = 1$). Causes of death reported as neurologic failure ($n = 8$), multisystem organ failure ($n = 7$), refractory hypoxemia ($n = 5$), refractory shock ($n = 1$), and cancer ($n = 1$).

Among children on invasive MV or full-face NIV at ARF-PARDS diagnosis, 19 children (22%) progressed to PARDS, which was associated with PICU admission source and lower initial SF ratio, but not demographic variables, comorbidities, nor PARDS trigger (**Supplemental Table 4**, http://links.lww.com/CCM/G784; and **Supplemental Table 5**, http://links.lww.com/CCM/G785). Neither blood products nor medications given on the day of ARF-PARDS diagnosis were associated with later progression to PARDS (**Supplemental Table 6**, http://links.lww.com/CCM/G786). In the multivariable model (n = 70), lower SF ratio at ARF-PARDS diagnosis was associated with progression to PARDS, and no other variables were retained.

Among children on HFO or nasal NIV at ARF-PARDS diagnosis, 47 (21%) were subsequently diagnosed with PARDS. Subsequent PARDS diagnosis was associated with pulmonary (nonasthma) comorbidity, higher initial FIO_2, lower initial SF ratio, and unfavorable subsequent vital signs (**Supplemental Table 7**, http://links.lww.com/CCM/G787; and **Supplemental Table 8**, http://links.lww.com/CCM/G788). Administration of blood products, diuretics, and parenteral nutrition on day 0 were also associated with subsequent PARDS (**Supplemental Table 9**, http://links.lww.com/CCM/G789). In the multivariable model (n = 155), lower SF ratio at ARF-PARDS diagnosis, higher subsequent heart rate, and diuretic administration on day 0 were significantly associated with increased odds of subsequent PARDS.

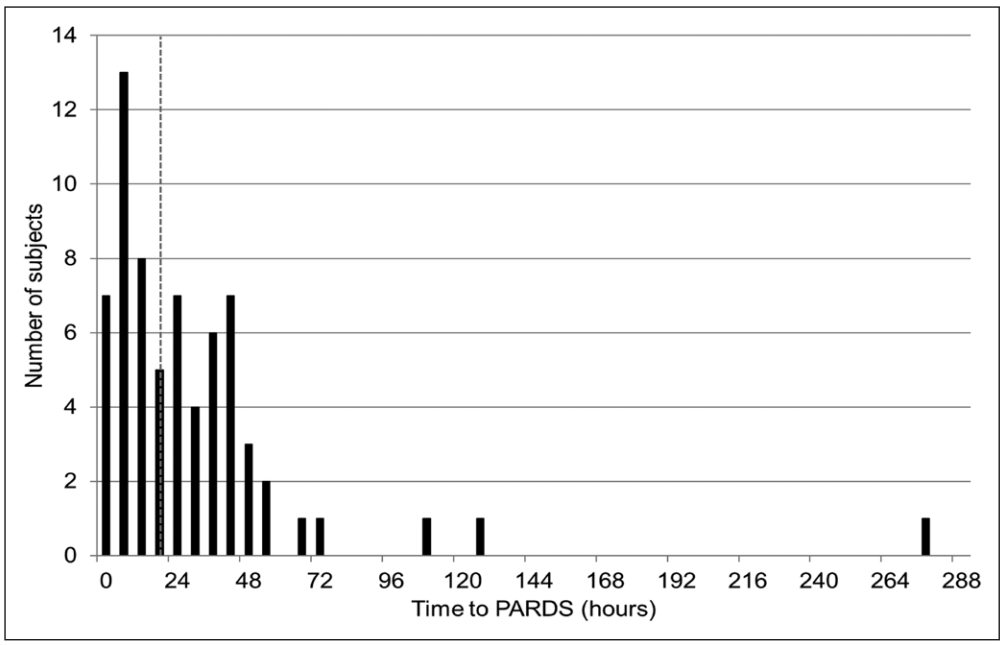

Figure 2. Interval from At Risk For Pediatric Acute Respiratory Distress Syndrome (ARF-PARDS) to Pediatric Acute Respiratory Distress Syndrome (PARDS) diagnosis. Subjects ($n = 66$) with subsequent PARDS were grouped based on the time between ARF-PARDS diagnosis and PARDS diagnosis. Each *bar* represents a 6-hr period (0–5.99, 6–11.99, etc.). The *dashed line* represents the median time between ARF-PARDS and PARDS diagnoses.

DISCUSSION

In this prospective international study, 4% of critically ill children admitted to participating PICUs

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TABLE 2.
Vital Signs Associated With a Subsequent Diagnosis of Pediatric Acute Respiratory Distress Syndrome Among All Subjects

Vital Sign	Progression to PARDS, $n = 66$	No Progression to PARDS, $n = 244$	p
Initial vital signs at ARF-PARDS diagnosis			
Heart rate (beats/min)	142 (114–167); $n = 47$	140 (118–156); $n = 181$	0.35
Respiratory rate (breaths/min)	39 (31–60); $n = 47$	40.50 (29.5–52); $n = 180$	0.72
Spo_2	96 (93–97); $n = 65$	95.00 (93–96); $n = 241$	0.36
Fio_2	0.60 (0.40–1.00); $n = 63$	0.40 (0.35–0.60); $n = 236$	< 0.01
SF ratio	155 (97–216); $n = 55$	230 (157–243); $n = 225$	< 0.01
Next vital signs after ARF-PARDS diagnosis			
Heart rate (beats/min)	134 (119.5–162); $n = 44$	129.5 (107–148); $n = 180$	0.047
Respiratory rate (breaths/min)	38.5 (29–57.5); $n = 44$	36 (26–49); $n = 179$	0.24
Spo_2	95 (93–97); $n = 55$	97 (95–98); $n = 218$	< 0.01
Fio_2	0.50 (0.40–0.65); $n = 55$	0.40 (0.30–0.50); $n = 215$	< 0.01
SF ratio	179 (140–240); $n = 46$	239 (188–313); $n = 150$	< 0.01
Change in vital signs after ARF-PARDS diagnosis			
Heart rate (beats/min)	3.5 (−11.5 to 13.5); $n = 44$	−8 (−21.5 to 6); $n = 180$	< 0.01
Respiratory rate (breaths/min)	−0.5 (−8 to 4.5); $n = 44$	−2 (−10 to 4); $n = 179$	0.61
Spo_2	0 (−1 to 2); $n = 55$	1 (0–3); $n = 218$	< 0.01
Fio_2	0.00 (−0.15 to 0.00); $n = 55$	0.00 (−0.10 to 0.00); $n = 215$	0.40
SF ratio	4 (−3 to 50); $n = 44$	4 (−2 to 53); $n = 148$	0.79

ARF-PARDS = At Risk For Pediatric Acute Respiratory Distress Syndrome, PARDS = pediatric acute respiratory distress syndrome, SF = ratio of Spo_2/Fio_2, Spo_2 = oxygen saturation.

Vital signs at ARF-PARDS diagnosis are all from within 2 hr of diagnosis. The "next" vital sign for each subject is the subsequent available measurement that was between 1 and 12 hr after the initial measurement. The "change" in vital sign is the initial measurement subtracted from the next measurement for each subject (i.e., next vital sign–diagnosis vital sign). Data are shown as median (interquartile range) with sample size for that cell. For the next vital signs, the median intervals between measurements were 5.5 hr (4.0–6.5 hr) for heart rate and respiratory rate, 4.0 hr (2.8–5.9 hr) for Spo_2, 4.0 hr (2.6–5.9 hr) for Fio_2, and 4.0 (2.5–6.0) for SF ratio.

met ARF-PARDS criteria and more than one in five of these patients were subsequently diagnosed with PARDS. PARDS diagnosis usually occurred more than 12 hours after ARF-PARDS diagnosis and was associated with higher mortality, fewer VFDs, and fewer PFDs. Taken together, these data suggest that trials testing strategies or therapeutics aimed at halting disease progression are likely feasible and warranted in this high-risk cohort of children.

Early identification and rapid treatment to decrease subsequent organ failure has become a focus of clinical and research strategies in adults with acute respiratory distress syndrome and critically ill patients of all ages with conditions including sepsis, traumatic brain injury, and post-bypass low cardiac output (4, 8, 13–17). Development of the ARF-PARDS criteria has laid the foundation for trials targeting similar prevention and early treatment in PARDS (2). In this study, we characterized this cohort of vulnerable pediatric patients, and several of our findings warrant consideration when planning such trials. First, children frequently met ARF-PARDS criteria before or upon PICU admission, so interventional PARDS prevention trials should consider screening for subjects across the hospital including the emergency department and general wards to identify all at-risk patients. Second, identifying potential subjects as early as possible is vital because the window to intervene before PARDS diagnosis is 12–48

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TABLE 3.

Multivariate Models of Factors Associated With Subsequent Pediatric Acute Respiratory Distress Syndrome (PARDS) Among All Subjects, Children on Nonnasal Support At Risk For (ARF)-PARDS Diagnosis, and Children on Nasal Support ARF-PARDS Diagnosis

	All Subjects		Children on Nonnasal Support		Children on Nasal Support	
Variable	Adjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Initial ratio of Spo_2/Fio_2	0.91 (0.85–0.97)	< 0.01	0.89 (0.79–1.00)	0.04	0.89 (0.82–0.96)	< 0.01
Initial heart rate	0.97 (0.77–1.22)	0.76	–	–	0.94 (0.73–1.21)	0.62
Next heart rate	1.27 (1.01–1.59)	0.04	–	–	1.35 (1.08–1.68)	0.01
Diuretics on day 0	4.82 (1.78–13.04)	< 0.01	–	–	4.71 (1.55–14.35)	< 0.01

OR = odds ratio.

All subjects: Model contains 204 subjects. Changes in vital signs are for each increase of 10 U relative to the mean value (initial ratio of Spo_2/Fio_2 [SF]: 207.1, initial hazard ratio [HR]: 138.2, next HR: 131.5). Use of total parenteral nutrition removed from the model due to low frequency. If heart rate is removed from the model, sample size increases to 269 and both initial SF ratio (adjusted OR [aOR], 0.91; 0.87–0.95;

$p < 0.01$) and diuretics (3.22; 1.64–6.37; $p < 0.01$) remain significantly associated with subsequent pediatric acute respiratory distress syndrome (PARDS).

Nonnasal subjects: Model contains 70 subjects. Changes in vital signs are for each increase of 10 U relative to the mean value (initial SF: 275.6).

Nasal subjects: Model contains 155 subjects. Changes in continuous variables are for each increase of 10 U relative to the mean value (initial SF: 184.5, initial HR: 141.9, next HR: 134.8). If heart rate is removed from the model, sample size increases to 202, and both initial SF ratio (aOR, 0.90; 0.85–0.95; $p < 0.01$) and diuretics (3.41; 1.39–8.37; $p < 0.01$) remain significantly associated with subsequent PARDS.

Dashes indicates that the variable was not included in that multivariate model.

hours in most patients. Third, PARDS prevention trials should enroll patients on HFO, NIV, or invasive MV because we observed that ~20% of ARF-PARDS subjects supported by each modality were later diagnosed with PARDS. These data also suggest some equipoise in respiratory modes to support children with ARF-PARDS. Fourth, trials are unlikely to be prognostically enriched by targeting children with specific PARDS triggers or chronic conditions, as these factors were not independently associated with subsequent PARDS. Finally, using our data for sample size calculations, approximately 400 subjects (200/arm) would be required to test if an intervention decreased the rate of subsequent PARDS by 50%, requiring multicenter collaborations or developing a pediatric network akin to PETAL.

This is the first multicenter study to estimate the prevalence of ARF-PARDS, and we found that the prevalence of ARF-PARDS (3.8%) is similar to those of cardiac arrest (4.2%) (18) and traumatic brain injury (3.3%) in critically ill children (19). Our observed prevalence of ARF-PARDS in North American subjects on respiratory support (6.7%) approached that of severe sepsis in children cared for in North American PICUs (7.7%) (20). The hospital-wide volume of ARF-PARDS is likely higher considering that general ward patients may also meet ARF-PARDS criteria as many centers use HFO outside the PICU, and the rate at which these children develop PARDS requires evaluation (21). Expert guidelines like those available for sepsis (14), cardiac arrest (18), and traumatic brain injury (15) may be warranted for ARF-PARDS once sufficient evidence is available and could help decrease practice variability.

We aimed to identify risk factors for subsequent PARDS. Lower initial SF ratio was the only variable consistently associated with subsequent PARDS, which is unsurprising as hypoxemia has been associated with unfavorable outcomes in previous cohorts of children with lung disease (1, 22, 23). Lower SF ratio was the one risk factor identified among children on nonnasal modes. Importantly, it is only those subjects who definitively had mild hypoxemia at ARF-PARDS diagnosis and then "progressed" to PARDS, as the degree of

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hypoxemia on nasal modes is not reliably measurable, which supports the reliability of SF ratio as a predictive marker. Increasing heart rate is also a plausible way to identify children progressing to PARDS for clinical or research purposes. But, the nasal patients in whom that association was observed require a clinician to initiate a nonnasal mode in order to be diagnosed with PARDS, and the influence of progressive tachycardia on clinician behavior may explain our findings. Similarly, diuretic administration may be a marker of treatment intensity more than a causative factor given its association with PARDS in only the nasal subgroup and the benefits of conservative fluid strategies in severe lung disease (24). Rates varying by geographic region could relate to differences in PICU admission criteria, diagnoses, or treatment strategies, although the rate of PARDS was similarly highest in North America in the main PARDIE study (1). Unlike a prior single-center study of children with bronchiolitis who met ARF-PARDS criteria, we did not find that younger children were at increased risk of subsequent PARDS (25). We also identified a lower rate of subsequent PARDS than the rate observed in that study (32%).

To our knowledge, this is the most comprehensive study of the epidemiology, risk factors, and outcomes of children meeting ARF-PARDS criteria to date. However, our study has several limitations. First, we did not enroll children not meeting ARF-PARDS criteria and measure their rate of subsequent PARDS, so we cannot determine whether the PALICC ARF-PARDS criteria truly identify "at-risk" children. However, the frequency of PARDS in our ARF-PARDS cohort (21%) is several-fold higher than the frequency reported in the general PICU population (3%), and we found only limited ways to improve predictability of PARDS, both of which suggest that the ARF-PARDS criteria successfully identifies a high-risk cohort (1). Second, some data were missing or unusable. However, we had sufficient data to construct models that identified risk factors for subsequent PARDS and showed that subsequent PARDS was independently associated with unfavorable clinical outcome. Third, we reported rates of subsequent PARDS across geographic regions, but small sample sizes may limit generalizability in some regions. Fourth, the PALICC definition does not allow children to meet PARDS criteria while on nasal modes, so we may have under-estimated the number of children who developed gas exchange impairments equivalent to PARDS. Given that more than half of our ARF-PARDS subjects were on HFO or nasal NIV, developing methods to diagnose PARDS on nasal support is essential, in part to prevent enrolling children who already have severely abnormal gas exchange in PARDS prevention trials. This idea, which has also been suggested by adult intensivists (26, 27), may be particularly important given increasing use of nasal modes for diseases ranging from critical bronchiolitis to coronavirus disease 2019 (28–30).

In conclusion, PICU patients who meet ARF-PARDS criteria are at high risk of subsequent PARDS, and there exists a 12–48-hour window of opportunity in which interventions to reduce progression to PARDS may be effective. Given the markedly worse outcomes associated with subsequent PARDS, interventional trials aimed at reducing subsequent PARDS are warranted and should screen all hypoxemic patients with a PARDS trigger and infiltrate on chest radiograph regardless of type of respiratory support modality or comorbid conditions.

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APPENDIX 1. V4 PARDIE INVESTIGATORS AND THE PALISI NETWORK

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