Epidemiology and Outcomes of Acute Respiratory Distress Syndrome in Children According to the Berlin Definition: A Multicenter Prospective Study*

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Objectives: In 2012, a new acute respiratory distress syndrome definition was proposed for adult patients. It was later validated for infants and toddlers. Our objective was to evaluate the prevalence, outcomes, and risk factors associated with acute respiratory distress syndrome in children up to 15 years according to the Berlin definition.

Design: A prospective, multicenter observational study from March to September 2013.

Setting: Seventy-seven PICU beds in eight centers: two private hospitals and six public academic hospitals in Brazil.

Patients: All children aged 1 month to 15 years admitted to the participating PICUs in the study period.

Interventions: None.

Measurements and Main Results: All children admitted to the PICUs were daily evaluated for the presence of acute respiratory distress syndrome according to the American-European Consensus Conference and Berlin definitions. Of the 562 patients included, acute respiratory distress syndrome developed in 57 patients (10%) and 58 patients (10.3%) according to the Berlin definition and the American-European Consensus Conference definition, respectively. Among patients with acute respiratory distress syndrome according to the Berlin definition, nine patients (16%) were mild, 21 (37%) were moderate, and 27 (47%) were severe. Compared with patients without acute respiratory distress syndrome, patients with acute respiratory distress syndrome had significantly higher severity scores, longer PICU and hospital length of stay, longer duration of mechanical ventilation, and higher mortality ($p < 0.001$). The presence of two or more comorbidities and admission for medical reasons were associated with development of acute respiratory distress syndrome. Comparisons across the three the Berlin categories showed significant differences in the number of ventilator-free days (21, 20, and 5 d, $p = 0.001$) and mortality for severe acute respiratory distress syndrome (41%) in comparison with mild (0) and moderate (15%) acute respiratory distress syndrome($p = 0.02$). No differences in PICU or hospital stay were observed across the groups.

Conclusions: The Berlin definition can identify a subgroup of patients with distinctly worse outcomes, as shown by the increased mortality and reduced number of ventilator-free days in pediatric patients with severe acute respiratory distress syndrome. (*Crit Care Med* 2015; 43:947–953)

Key Words: critical care; epidemiology; pediatrics; respiration, artificial; respiratory distress syndrome, adults; respiratory insufficiency

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Since first described by Ashbaugh et al (1) in 1967, acute respiratory distress syndrome (ARDS) has been recognized as a burden for critically ill patients, as demonstrated by the increased ventilatory requirements and high mortality. In

1994, the American-European Consensus Conference (AECC) first defined the diagnostic criteria for ARDS, which has been widely used by pediatric and adult critical care clinicians and has led to major advances in the understanding of the epidemiology, outcomes, and treatment of the disease (2). In 2012, American and European Intensive Care Societies reviewed the AECC criteria to address some of its limitations. The new criteria, named as the Berlin definition, was established through a consensus of experts and validated using patient-level meta-analysis of 4,188 adult patients with ARDS (3). It classified patients with ARDS into three mutually exclusive categories—mild, moderate, and severe—and showed a clear distinction in severity across them.

Although the epidemiology of ARDS has been well documented for adults, few epidemiological studies have been conducted with children. Studies that used the AECC definition have shown prevalence from 0.86% to 7.8% of PICU admissions (4–10) and 5% to 20.5% of ventilated patients (5, 8, 9, 11–13), with mortality rates ranging from to 14% to 61% (4, 14). Higher mortality rates have been reported in developing countries (4, 6, 7, 10).

Despite the fact that the data used in the Berlin study did not include pediatric patients, its validity for infants and toddlers has recently been demonstrated in a study conducted by the European Society for Pediatric and Neonatal Intensive Care (13). The applicability of the Berlin definition for children older than 18 months, however, has not been evaluated yet.

The main objective of this study was to evaluate whether the use of the Berlin definition can better discriminate the severity of the disease in comparison with the AECC definition, by analyzing the differences in mortality, number of ventilator-free days (VFD), and hospital and PICU length of stay (LOS) in a population of children from 1 month to 15 years old. We also aimed to evaluate the prevalence of ARDS, to evaluate the importance of selected risk factors for its development, and to report the ventilatory practices and rescue therapies used in our population of critically ill children in a developing country.

METHODS

We conducted a prospective, multicenter cohort study from March to September 2013. The study protocol was approved by the Committee of Ethics on Research at each participating center, and informed consent was obtained from the parents or legal guardians of all the participants.

Eight centers participated in the study, comprising a total of 77 PICU beds. All the centers were located in two metropolitan cities in the state of Sao Paulo, Brazil. Among the participating centers, two were private tertiary hospitals and six were public academic hospitals—two secondary and four tertiary centers. All consecutive children from 1 month to 15 years old admitted to the participating PICUs during the study period were eligible for the study. Patients who died within the first 24 hours of PICU admission, who had cyanogenic heart defect, or who did not consent to participate were excluded.

Data Collection

Clinical and demographic data, severity scores (Pediatric Risk of Mortality [PRISM] and Pediatric Index of Mortality [PIM] 2), type of admission (medical or surgical), maternal years of schooling (used as a surrogate for socioeconomic status), and presence of infection were registered at PICU admission. Data on the presence of pulmonary edema on chest radiograph, ventilator settings, blood gas analysis, and the presence of the diagnostic criteria for ARDS according to the Berlin and AECC definitions were registered daily, from the day of admission to PICU discharge or death. Additional data on the etiologic agent of infection, duration of mechanical ventilation, length of PICU and hospital stay, and mortality were registered at PICU and hospital discharge. For patients in whom ARDS developed, we also recorded information about the risk factor for ARDS, presence and etiologic agent of infection that led to ARDS, rescue therapies, and number of VFD. We used the worst Pao_2/Fio_2 registry during PICU stay to categorize ARDS according to both definitions, along with the positive end-expiratory pressure (PEEP), peak inspiratory pressure, tidal volume (Vt), pH, and Pco_2 values recorded at the same moment. Comorbidity was defined as the presence of any chronic condition prior to PICU admission and classified according to the affected system as malformations, genetic syndromes, neuromuscular, cardiovascular, respiratory, gastrointestinal, renal, immunologic, metabolic, oncohematologic disease, and prematurity. Respiratory system compliance (Crs) was calculated according to the formula: Vt divided by the driving pressure (peak inspiratory pressure – PEEP), and oxygenation index (OI) was calculated as follows: Mean airway pressure × Fio_2 divided by Pao_2. Vt was registered as mL/kg of actual body weight. Although compensation of the circuit is a current practice among the participating PICUs, it was not compulsory. Prevalence of ARDS was computed as the ratio of the number of patients diagnosed as ARDS to the number of patients admitted to the study. Protective ventilation was defined as ventilation with Vt up to 6 mL/kg and plateau pressure up to 30 cm H_2O. Sepsis and septic shock were defined according to the 2005 International Pediatric Sepsis Consensus Conference (15). Malnutrition was classified according to the Bulletin of the World Health Organization (16) and obesity according to the Centers for Disease Control and Prevention growth charts (17).

Quality Control

Investigators were trained by the study team in the published clinical vignettes to evaluate the primary cause of respiratory failure (18). A radiologist provided training on the interpretation of chest radiographs for the diagnosis of pulmonary edema according to the original Berlin publication and added some pediatric radiographic examples of pulmonary edema to the training. In the beginning of the study, the researchers provided a report of all the chest radiographs performed in their PICU in a prespecified date, regarding the presence of pulmonary edema. The results were compared to the same assessment provided by a blinded radiologist. If the difference between a specific center and the radiologist's report was at least 20%, all the researchers from that center were asked to repeat the training on the interpretation of the chest radiographs. The κ coefficient of the chest radiograph reads by the radiologist and the researchers was 0.853.

Statistical Analysis

Clinical and demographic data are described for all patients included in the study. Continuous variables are expressed as median and interquartile ranges (IQRs) and categorical variables as frequencies and percentages. Continuous data were compared using Mann-Whitney or Kruskal-Wallis tests and categorical data by the Pearson chi-square or Fisher exact test. Variables showing significant associations were analyzed by tests of multiple comparisons corrected by Bonferroni. Survival analysis was done using Kaplan-Meyer curves and log-rank test, whereas survival at 60 days after PICU admission was analyzed using a Cox proportional hazards regression model. A two-sided p value up to 0.05 was considered significant. Statistical analysis was performed using SPSS (SPSS Statistics for Windows, V17; Chicago, IL).

RESULTS

During the study period, 661 patients were admitted to the participating PICUs and 562 were included in the study, as shown in **Figure 1**. Of the 562 included patients, 315 (56%) were male patients, with median age of 12.6 months (4.8–58.8 mo). Four hundred and fifty patients (80%) had normal weight for height, whereas 92 (16%) had malnutrition and 3.6% were obese. PRISM score and PIM 2 risk were 7 (4–11) and 1.3% (0.7–4), respectively. Most of the patients (65%) had at least one prior comorbidity and 435 (77%) were admitted for medical reasons. Infectious conditions were responsible for 337 PICU admissions (60%), and in 280 of them (83%), the source of the infection was the respiratory system. A total of 343 patients (61%) underwent ventilatory support, either invasive or noninvasive. Mechanical ventilation was used in 295 (52%) patients, with median duration of 2 days.

Among the 562 included patients, the prevalence of ARDS according to the Berlin definition at any time of PICU stay was 10% (57 ARDS cases). Among mechanically ventilated patients, the prevalence of ARDS at any time during PICU stay was 19.3%. Thirty-two patients fulfilled the ARDS criteria at admission and 25 developed ARDS after the first day.

Comparisons between ARDS and non-ARDS patients using the Berlin definition are shown in **Table 1**. Compared with patients without ARDS, patients with ARDS had higher severity scores, longer PICU and hospital LOS, longer duration of mechanical ventilation, and higher mortality ($p < 0.001$). The presence of two or more comorbidities and admission for medical reasons were associated with the occurrence of ARDS ($p < 0.03$).

When patients were classified according to both definitions, 58 met the AECC criteria for acute lung injury (ALI)/ARDS and 57 met the Berlin criteria. One patient with ALI could not be diagnosed as ARDS according to the Berlin definition due to the lack of PEEP/continuous airway positive pressure at least 5 cm H_2O. The distribution of the patients according both definitions is shown in **Table 2**. Significant differences in VFD were observed using both classifications, whereas differences in mortality were observed only for the Berlin classification.

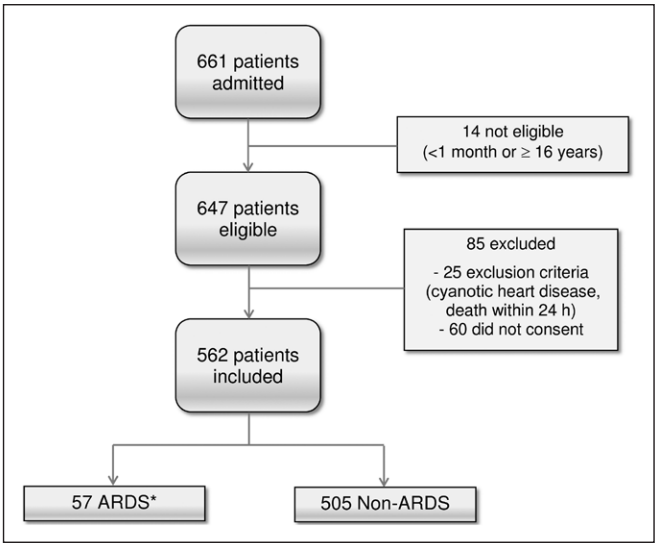

Figure 1. Flow chart of the admitted patients. *Acute respiratory distress syndrome (ARDS): according to the Berlin definition.

Comparisons Across the Berlin Categories

Comparisons across the Berlin categories are shown in **Table 3**. We did not observe any difference in PICU or hospital LOS across the three ARDS categories. Significant differences were observed in the number of VFD and OI for severe ARDS in comparison to mild and moderate ARDS ($p = 0.001$). Mortality was also higher for patients with severe ARDS when compared with patients with mild ARDS ($p = 0.02$). Because there were no deaths in the mild ARDS group, Cox model was adjusted by grouping the mild and moderate patients into one category and comparing them with the severe patients. Kaplan-Meyer curves for mortality at 60 days after PICU admission are shown in **Figure 2**. Comparisons using the log-rank test showed significant survival differences between the patients with mild/moderate ARDS in comparison with patients with severe ARDS ($p = 0.02$). Unadjusted analysis using Cox regression showed lower survival at 60 days for patients with severe ARDS compared with patients with mild/moderate ARDS (hazard ratio [HR] = 3.85; 95% CI, 1.07–13.84; $p = 0.039$). After adjustment for covariates, statistically significant differences were no longer observed, but there was a trend toward lower survival for severe ARDS, with HR =3.34 (95% CI = 0.88–12.67; $p = 0.07$).

Characteristics of Patients With ARDS

For patients with ARDS, the most frequent reported comorbidities were respiratory conditions (26%), prematurity (19.3%), gastrointestinal disorders (12.3%), and genetic diseases (10.5%). Reported risk factors for ARDS included pulmonary sepsis/septic shock in 26 patients (46%), pulmonary infection without sepsis in 19 patients (33%), and nonpulmonary sepsis/septic shock in six patients (11%). Median time from the occurrence of the risk factor and the development of ARDS was 3 days (IQR, 2–5 d). Fifty-one ARDS episodes (89%) had infectious etiology, 45 of them (79%) from pulmonary source. For patients with moderate ARDS, causes of death

TABLE 1. Clinical and Demographic Characteristics and Outcomes in Patients With and Without Acute Respiratory Distress Syndrome According to the Berlin Definition

	Non-ARDS (*n* = 505)	ARDS (*n* = 57)	*p*
Age in months[a]	12.5 (5–59)	14.4 (1–211)	
< 12 mo (%)	247 (49)	26 (46)	0.99
12–60 mo (%)	132 (26)	19 (33)	
> 60 mo (%)	125 (25)	12 (21)	
Male, *n* (%)	284 (56)	31 (54)	0.77
Nutritional status, *n* (%)			
Normal weight	409 (81)	41 (72)	0.12
Malnutrition/severe malnutrition	80 (16)	12 (21)	
Obesity	16 (3)	4 (7)	
Pediatric Risk of Mortality[a]	6.5 (4–9)	12.5 (8–15)	< 0.001
Pediatric Index of Mortality 2[a]	1.2 (0.6–3.3)	4.0 (13–8.7)	< 0.001
Comorbidities			
None	185 (37)	14 (25)	0.03
1 comorbidity	279 (55)	33 (58)	
2 or more comorbidities	41 (8)	10 (18)	
Nature of admission (%)			
Medical	379 (75)	56 (98)	< 0.001
Scheduled surgery	102 (20)	0 (0)	
Urgent surgery	24 (5)	1 (2)	
Mother schooling (%)			
Unknown	100 (20)	12 (21)	0.98
1–8 yr	187 (37)	20 (35)	
9–11 yr	162 (32)	18 (32)	
≥ 12 yr	55 (11)	7 (12)	
PICU LOS, days[a]	5 (3–9)	12 (9–19)	< 0.001
Hospital LOS, days	13 (7–23)	22.5 (14–36)	< 0.001
Duration of mechanical ventilation[a]	1 (0–5)	10 (16–17.2)	< 0.001
Mortality (%)	20 (3.9)	14 (24.5)	< 0.001

ARDS = acute respiratory distress syndrome, LOS = length of stay.
[a]Values are expressed in medians and interquartile range.

were multiple organ dysfunction syndrome (MODS) in one patient and brain death in two patients, whereas for patients with severe ARDS, the causes of death were refractory hypoxemia in five patients, refractory shock in three patients, and MODS in three patients. Mortality was higher in tertiary hospitals in comparison with secondary hospitals (38% and 10%, respectively, $p = 0.04$).

Ventilatory Practices and Adjunctive Therapies

Ventilatory practices were analyzed on days 1, 3, 5, and 7 of the ARDS diagnosis and on the day of extubation. Of the 235 ventilator days analyzed, the ventilatory modes most frequently used were as follows: pressure control in 194 ventilator days (82.5%), pressure-regulated volume control in 27 ventilator days (11.4%), volume control in 5 ventilator days (2.1%), high-frequency oscillatory ventilation (HFOV) in 4 ventilator days (1.7%), and others in 5 ventilator days (2.1%). Pulmonary recruitment maneuvers were used in 20 of the patients (35%) and prone position in 25 (43%). Thirty-six patients (63%) received corticosteroids: three (5.2%) for treatment of the ARDS and 33 (57%) for treatment of the primary disease. Protective ventilation was indicated by the medical staff in 40 patients (70%), but only 19 patients (33%) were ventilated with protective strategies. Five patients received HFOV during any time of the ventilation period. Therapies such as pulmonary surfactant, HFOV, extracorporeal membrane oxygenation (ECMO), tracheal gas insufflation, and inhaled nitric oxide were considered necessary by the attending physicians in 33 occasions, but actually administered in 22. One possible reason for the nonadministration of the prescribed treatments could be the lack of resources—nitric oxide was available in seven centers, HFOV in one center, and none of the centers had an ECMO service.

DISCUSSION

Our study shows that although the use of the Berlin definition did not significantly change the number of cases diagnosed as ARDS in critically ill children in comparison with the AECC definition, it better discriminates the differences in severity of the disease among patients with ARDS. This was shown by the higher mortality and the reduced number of VFD in the subgroup of patients with Pao_2/Fio_2 less than 100. The differences in severity did not influence PICU and hospital LOS. We also observed a high prevalence of ARDS in our population of critically ill children.

While in the population included in the Berlin study, the increase in severity of ARDS was consistently associated with increased mortality, duration of mechanical ventilation, and reduced number of VFD, we observed significant differences in survival and VFD only for severe ARDS group when compared with the mild and mild/moderate groups. In a recent study that evaluated the validity of the Berlin definition in infants and toddlers, the authors also showed an increased mortality and need for ECMO only for patients with severe ARDS when compared with patients with mild and moderate ARDS (13). As in our study, they did not find any difference PICU LOS across the three groups. Differences in mortality only for patients with severe ARDS have also been reported in a prospective study conducted with adults (19). These results suggest that the Berlin definition can identify a subgroup of

TABLE 2. Distribution and Outcomes of the Patients According to the American-European Consensus Conference and the Berlin Definitions

	American-European Consensus Conference (*n* =58)			Berlin Definition (*n* =57)			
	Acute Lung Injury	Acute Respiratory Distress Syndrome	*p*	Mild	Moderate	Severe	*p*
n (%)	10 (17)	48 (83)		9 (16)	21 (37)	27 (47)	
Ventilator-free days	22 (20–24)	14 (0–20)	0.003[a]	22 (20–23)	20 (14–21)	5 (0–17)	0.001[b]
Mortality (%)	0 (0)	14 (29)	0.098[c]	0 (0)	3 (14)	11 (41)	0.002[c]

[a]Mann-Whitney test.
[b]Kruskall-Wallis test.
[c]Fisher exact test.
Values expressed in medians and interquartile range.

patients—those with severe ARDS—with clearly worse outcomes than the mild and moderate ARDS.

Previous studies that used the AECC definition have shown variable prevalence rates of pediatric ALI/ARDS. Few epidemiological data on pediatric ARDS in developing countries, however, have been published so far. Four studies conducted in China showed prevalence of ARDS from 0.9% to 7.8% of PICU patients, with mortality ranging from 44.8% to 61% (4, 6, 7, 10). Our study showed a higher prevalence of ARDS (10%) at any stage of PICU stay. We speculate that some characteristics of our hospitals and population may have contributed to the high prevalence of ARDS among our patients. First, due to the shortage of PICU beds in the two academic tertiary centers that most contributed with ARDS cases, some less severe patients could be ventilated in other areas than the PICU, such as the emergency department or step down units, which may have selected more severe patients to be admitted to the PICUs. Second, the daily register of blood gas results and chest radiographs of all the admitted patients, instead of only those who were diagnosed with ARDS by the medical staff, may have prevented the underdiagnosis of ARDS, which has been shown to represent up to 73% of pediatric ARDS cases (9). Finally, the high frequency of infectious diseases (60% of the total PICU population, 90% of the patients with ARDS) may have contributed for the high prevalence of ARDS. In spite of the differences in the prevalence rates reported in previous studies, we believe that the attention to quality control and the similarities with previously reported outcomes assure the reliability of our data.

This is, to our knowledge, the first prospective study that applied the Berlin definition to evaluate the prevalence and outcomes of pediatric ARDS in children older than 18 months,

TABLE 3. Comparisons Across the Berlin Categories

	Mild (*n* = 9)	Moderate (*n* = 21)	Severe (*n* = 27)	*p*
Hospital LOS	19 (13–21)	20 (18–36)	26 (15–37)	0.667
PICU LOS	11 (8–19)	12 (9–15)	15 (11–20)	0.538
Ventilator-free days	22 (20–23)	20 (14–21)	5 (0–17)[a,b]	< 0.001
Mortality (%)	0 (0)	3 (15)	11 (41)[a]	0.026
Pao_2/Fio_2	228 (211–235)	127 (109–144)[a]	70 (56–80)[a,b]	< 0.001
Oxygenation index	5.6 (4.7–7.6)	9.6 (7.5–13.1)	26 (17.1–37)[a,b]	< 0.001
pH	7.4 (7.2–7.4)	7.4 (7.3–7.4)	7.4 (7.3–7.4)	0.103
Pco_2	52 (49–55)	52 (45–57)	51 (49–69)	0.967
Positive end-expiratory pressure (cm H_2O)	7 (6 7)	8 (7–10)[a]	10 (9–14)[a,b]	< 0.001
Peak inspiratory pressure (cm H_2O)	26 (22–28)	25 (21–29)	32 (28–35)[a,b]	0.001
Tidal volume (mL/kg actual body weight)	6.0 (4.8–7.0)	8 (6.0–9.0)[a]	7.0 (6.0–8.0)	0.044
Respiratory system compliance	0.35 (0.31–0.46)	0.44 (0.36–0.57)	0.35 (0.31–0.53)	0.354

LOS = length of stay.
[a]Bonferroni $p < 0.05$, compared with mild.
[b]Bonferroni $p < 0.05$, compared with moderate.
Values are expressed in median and interquartile range.

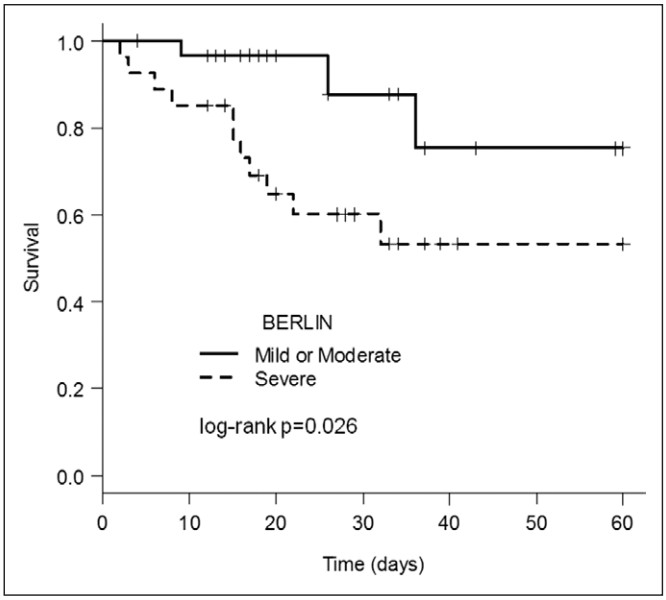

Figure 2. Kaplan-Meyer curves showing survival at 60 d after PICU admission for mild/moderate and severe acute respiratory distress syndrome.

adding new information on the validity of the Berlin definition in a wider age group. We also showed a very high prevalence of ARDS in our population of critically ill children in the southeast of Brazil. As discussed by other authors, multicenter and maybe international collaborative studies are still necessary to elucidate the similarities and regional differences in the epidemiology and outcomes of ARDS in different pediatric populations all over the world (20).

Some limitations of this study, however, should be acknowledged. First, the small sample size made our study underpowered to rule out differences in survival across the three groups. Second, in our study, the compensation of the ventilator circuit was not standardized. This must be taken into account when interpreting the comparisons in Vt and Crs across the Berlin categories. Third, due to its strictly observational nature, it is possible that not only the ARDS severity but also the different ventilation strategies and monitoring policies across the centers may have influenced the outcomes. Finally, this study was conducted during the autumn and winter seasons, when there is a marked increase in the prevalence of respiratory infections in the Southeast of Brazil, mainly of respiratory syncytial virus bronchiolitis and pneumonia, which may have influenced the prevalence of ARDS in our sample.

CONCLUSIONS

Our study suggests that the Berlin definition can better discriminate the severity of ARDS in children in comparison with the AECC definition, as shown by the decreased survival and reduced number of VFD in patients with severe ARDS compared with patients with mild and moderate ARDS. It also demonstrated a high prevalence of ARDS in this sample of critically ill children in the southeast of Brazil. Further studies are necessary to better understand the applicability of the Berlin definition in the pediatric population, as well as the epidemiology of pediatric ARDS and the impact of the distribution of health services resources in the outcome of ARDS children in developing countries.

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