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Bruno Kenzo Harada *

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Research Article

Pediatric Acute Respiratory Distress Syndrome (Pards) In Sepsis Patients with Chronic Conditions: An Adaptation of the Phoenix Score and Palicc-2 In Chronically Ill Children and Adolescents

Bruno Kenzo Harada [1*], Francisco Soriano Garcia [2], Michele Luglio [3], Werther B. de Carvalho [4], Artur F. Delgado [4]

[1] School of Medicine, University of São Paulo, SP, Brazil.

[2] Department of Emergency Medicine, University of São Paulo Medical School, São Paulo, Brazil.

[3] Pediatric Critical Care Center, Child and Adolescent Institute, Hospital das Clínicas, Faculty of Medicine, University of São Paulo, São Paulo, SP, Brazil.

[4] Pediatric Critical Care Center, Child and Adolescent Institute, University of São Paulo School of Medicine Hospital das Clínicas, São Paulo, SP, Brazil.

***Corresponding Author:** Bruno Kenzo Harada, School of Medicine, University of São Paulo, SP, Brazil.

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Abstract:

Background. acute respiratory distress syndrome (ARDS) remains a significant cause of morbidity and mortality in the pediatric intensive care unit. This case series describes five cases in a population of chronically and critically ill children, all of whom presented with a primary infectious insult (sepsis or septic shock) that led to ARDS between 2020 and 2022. Acknowledging the complex interplay between these two clinical entities, the study aimed to simultaneously apply the most recent diagnostic guidelines for ARDS (PALICC-2) and pediatric sepsis (Phoenix criteria) to support these clinical findings, especially in that specific population, with current literature.

Material-Methods. Retrospective analysis of medical records from five selected patients and application of both PALICC-2 and Phoenix sepsis score to cases identified having simultaneously PARDS after an infectious insult, utilizing clinical and laboratorial information presented at the time.

Results. After scores application, our descriptive case studies demonstrated patients with both diagnoses were chronically infected and exhibited a baseline infectious pattern as the cause of mild/moderate PARDS, exhibiting clinical correlation with score values obtained.

Conclusions: Appropriate correlation between clinical findings and severity scores.

Key words: pediatric acute respiratory distress syndrome (PARDS); septic shock; sepsis, chronic; children and adolescents; Phoenix Score and Palicc-2

Introduction

Acute respiratory distress syndrome (ARDS) was first documented by Ashbaugh et al. in 1967 (1). Out of 272 patients on artificial ventilatory support, 12 developed ARDS, characterized by refractory hypoxemia despite increased fractions of inspired oxygen (FiO2), which only improved with positive end-expiratory pressure (PEEP). This clinical presentation included respiratory failure, cyanosis, reduced pulmonary compliance, and diffuse bilateral infiltrates on chest radiography. Seven of these 12 patients died. Autopsies revealed a consistent histopathological pattern of microatelectasis, vascular congestion, hemorrhage, pulmonary edema, and hyaline membranes [1].

Initially, ARDS was defined as “adult respiratory distress syndrome” [2]. However, it has become evident that patients in pediatric intensive care units (PICUs) could also exhibit a similar systemic syndrome, despite the

morphofunctional differences associated with incomplete development of the pulmonary parenchyma and other structures, depending on the age of the individual (4-8). Using the criteria established for adults, the Pediatric Acute Lung Injury Consensus Conference (PALICC) in 2015 defined pediatric ARDS as a syndrome characterized by hypoxia and a new pulmonary inflammatory infiltrate developing within seven days of a known lung insult. Hypoxia was graded based on the Oxygenation Index (OI) as mild, moderate, or severe (4–8, 8–16, and >16, respectively) or alternatively, according to the Berlin criteria using the PaO2/FiO2 ratio (1,3). In 2023, an update to the PALICC-2015 criteria was published by Emeriaud et al. and will be used in the current study [9].

Given the evolving diagnostic criteria for ARDS, epidemiological studies have shown variability depending on the guidelines used. Meta-analyses applying the AECC or Berlin criteria reported an incidence ranging from 2 to 12.8 cases per 100,000 person-years in data from the United States, Australia, and New Zealand. In PICUs, the incidence of ARDS is

1-4% in admitted patients and 8–10% in those on mechanical ventilation [6, 8]. Studies using both criteria concurrently estimated an incidence of 3.5 cases per 100,000 person-years and 2.3% in PICU patients [3,4]. The mortality rate among hospitalized ARDS patients ranges from 35.3% to 46.1%, underscoring the severity of this condition in critically ill pediatric patients [9].

In the pediatric population, the most prevalent direct cause of PARDS is infectious pneumonia, accounting for 35% (5, 6) to 58% [7] of the cases. Sepsis is the most frequent

indirect cause, accounting for 13% [5]-32% (6) of the cases. Given the focus of this study, greater emphasis was placed on sepsis as an indirect etiology.

The definitions of "systemic inflammatory response syndrome (SIRS)," "sepsis," "septic shock," and "multiple organ dysfunction syndrome" stem from the Pediatric Sepsis Consensus Conference organized by the American College of Critical Care Medicine and Society of Critical Care Medicine in 2002 have been changed. Sepsis was defined as the presence of SIRS alongside an infection, with SIRS requiring two of the following four criteria: abnormal body temperature (>38.5°C or <36°C), tachycardia, tachypnea, or leukocyte count abnormalities [8,10]. Diagnosis of infection involves characteristic clinical signs such as petechiae, purpura, hemodynamic instability, and pulmonary infiltrates (8). Severe sepsis was defined as sepsis with concurrent cardiovascular or respiratory dysfunction, whereas septic shock was defined as sepsis with cardiovascular dysfunction indicated by tachycardia and peripheral hypoperfusion with no response to volume administration or the use of vasoactive medications (8).

In 2024, a new international consensus introduced the Phoenix score for the diagnosis of pediatric sepsis and septic shock. This score accounts for age-related differences in vital signs, immune function, comorbidities, clinical presentation, and outcomes. Sepsis is defined by a Phoenix score ≥2 points, indicating significant multisystem organ dysfunction in children with suspected or confirmed infection. Septic shock is characterized by a score ≥1 in the cardiovascular component, reflecting severe hypotension, serum lactate >5 mmol/L, or vasoactive drug requirement (10). In this context, the present study aimed to provide a descriptive analysis and exemplify the application of two risk stratification systems—PALICC-2 for Pediatric Acute Respiratory Distress Syndrome (PARDS) and Phoenix for sepsis/septic shock—in the population admitted to the Pediatric Intensive Care Unit of the Instituto da Criança, Hospital das Clínicas, Faculty of Medicine, University of São Paulo. This is a tertiary care center specialized in the management of highly complex cases and chronically ill patients.

Materials and Methods

This retrospective study analyzed some medical records of patients admitted between 2020 and 2022. The search employed the keywords “acute respiratory distress syndrome,” “respiratory distress syndrome,” “Shock Lung,” and “Acute Lung Injury” as discharge diagnoses. From these discharge diagnoses, the selected medical records were further examined to identify cases in which sepsis was documented as the etiology of pulmonary involvement.

In addition to identifying sepsis as the cause of PARDS, this study aimed to identify cases of suspected or confirmed infection at admission or during hospitalization. A suspected infection was defined as a classical clinical presentation accompanied by positive markers of acute inflammation (e.g., elevated C-reactive protein and hematological changes such as leukocytosis and neutrophilia) but lacking microbiological confirmation via blood culture [8].

Similarly, confirmed infection was defined as a clinical presentation consistent with infection, positive acute inflammatory markers, and microbiological confirmation of the infection [8].

From the selected medical records, analyzed variables included age, sex, PIM2 Score, Phoenix Score, PALICC-2022 criteria, comorbidities at ICU admission, etiology of PARDS, and severity grade of PARDS at the time of diagnosis. Regarding the analysis of PARDS specifically, the PaO2/FiO2 and SatO2/FiO2 ratios were examined at the time of diagnosis based on the following parameters: PaO2 (arterial oxygen pressure), SatO2 (oxygen saturation via pulse oximetry), and FiO2 (inspired oxygen fraction) [8, 9, 10].

Phoenix Score

The Phoenix Score is part of the new international consensus for the pediatric population regarding the diagnosis of sepsis and septic shock. Published in 2024 by Schlapbach et al. [10], the new definitions are based on age-related variabilities compared to adults, including differences in vital signs, immune function development, comorbidities in clinical presentations, and the epidemiology and outcomes of these conditions. According to the new resolution, sepsis identified using the Phoenix criteria is determined by a score of two or more points, indicating significant multisystem organ dysfunction, which may involve the respiratory, cardiovascular, neurological, or coagulation systems in children with suspected or confirmed infection. Septic shock in this population is defined by the presence of suspected infection and one point in the cardiovascular component of the Phoenix Score, which is associated with severe age-specific hypotension, a serum lactate level above 5 mmol/L, or the need for vasoactive drugs. For the purposes of this study, the cutoff value adopted in the cardiovascular system was set at 1 [10].

PIM2 Score

The PIM2 Score was calculated based on data from the medical records of the selected patients at the time of admission to the intensive care unit [25].

PALICC – 2022

The diagnosis must adhere to the criteria defined by the 2022 PALICC guidelines [9]. The cut-off value used for severity parameters was primarily based on the SatO2/FiO2 ratio, which was more readily applicable to all patients. The selected threshold was set at 265 because this value has been shown to correlate with mortality in the study by Khemani et al. [11].

Initial Patient Selection

Initial patient selection was conducted using ICD codes, specifically employing discharge diagnoses defined as J80 and J81 [24]. This search yielded seven patients with chronic diseases and acute respiratory involvement.

The medical records of the selected patients were analyzed, with the primary inclusion criterion being adherence to the 2022 PALICC criteria [9]. Five patients met the inclusion criteria. Subsequently, the Phoenix score was applied using data from the day of PARDS

diagnosis to determine the infectious etiology of the respiratory condition. Simultaneously, PIM2 severity score data were collected at the time of admission to the intensive care unit.

Additional data were gathered for the study, guided by an analysis of the patients' clinical presentations and clinical-laboratory characteristics, including cultures and viral panels, as well as the antibiotic regimens administered during the entire hospitalization period.

All patients analyzed had pre-existing chronic conditions, which determined the pattern of chronic admission to the emergency and intensive care departments, either due to decompensation of the underlying condition or clinical complications resulting from frequent admissions. In all the selected cases, the profile of decompensation or its association with the underlying disease was ruled out during the diagnostic investigation. Table 1 summarizes the medical history of the previous diagnoses for each patient.

		• Reaction to the rotavirus vaccine requiring intestinal resection • Protein-energy malnutrition
D	• VACTERL syndrome with recurrent upper respiratory tract infections and worsening of bronchial secretion	• Congenital malformations: esophageal atresia, ventricular septal defect, limb malformation, and vertebral malformation • 4 previous cardiorespiratory arrests due to structural epilepsy
And	• Respiratory failure and shock	• Congenital nephrotic syndrome, underwent kidney transplant with chronic rejection and development of B lymphoblastic lymphoma

Table 1: Relationship between the patients (A, B, C, D, and E) and their respective clinical histories.

Results

A retrospective review of medical records identified seven patients, including their respective readmissions, based on discharge ICD codes J80 and J81. Among these, only five met the PALICC-2 diagnostic criteria for pediatric acute respiratory distress syndrome (PARDS) [9].

The study included pediatric patients with a diagnosis of PARDS who met the following criteria: admission to our pediatric intensive care unit between January and December 2022; age between 1 month and 18 years and a diagnosis of sepsis or septic shock with Phoenix score [10]. Conversely, patients with a diagnosis of PARDS from other etiologies were excluded.

These five patients were selected for the study, and their clinical data were the focus of medical record analysis. For the reason that the present study is a descriptive case series, no statistical analyses were performed.

The most common initial presentation in all patients was a clinical syndrome of acute respiratory distress accompanied by hypoxemia, either refractory or responsive to oxygenation measures. All patients had chronic clinical conditions with acute respiratory deterioration.

The next step in the review of medical records was to assess PARDS severity. The analysis focused on clinical parameters such as SatO2, FiO2 and SatO2/FiO2 ratios. These parameters were chosen because they were the most consistently available across the clinical records of all patients. Notably that only one patient (Patient D) received mechanical ventilation during the hospitalization period. To ensure the consistency of the analyzed data, the aforementioned parameters were prioritized, as summarized in Table 2.

Patient	SatO2	FiO2	SatO2/FiO2
A	95	50	190
B	92	35	262
C	92	40	230
D	85	40	212
E	88	50	176

Table 2: Oxygen saturation by pulse oximetry (SatO2); inspired oxygen fraction (FiO2); ratio of SatO2 to FiO2 (SatO2/FiO2). A, B, C, D, and E: patients selected for the study.

In these patients, the infectious etiology of the syndrome, such as sepsis and septic shock, was also investigated, resulting in a smaller number of patients selected for the case series. Infectious etiology was considered in the presence of suspected or confirmed infection at admission or during hospitalization. Accordingly, the Phoenix score was applied to the patients and the results are presented in Table 3.

Patient	*Phoenix Score*	*FiO2*	*Lactate*	*INR*	*Glasgo w*	*Platelets*
A	**3**	50%	15	1,22	>10	216.000
B	**1**	40%	NOT PERFO RMED	1,3	>10	487.000
C	**1**	40%	NOT PERFO RMED	NOT PERFO RMED	>10	438.000
D	**4**	80%	35	1,22	>10	32.000
E	**4**	100%	114	2,48	>10	6.000

Table 3: Phoenix score and its constituent parameters. A, B, C, D, and E: patients selected for the study.

It is noteworthy that in all patients, throughout their hospitalization periods, owing to the acute infectious cause, pathogen screening was performed for both bacterial and viral pathogens using different methods such as blood culture, urine culture, sputum culture, and viral panel. The tests were negative or showed the presence of polymicrobial growth, which hindered specific analysis and was consistent with previous cultures suggestive of normal flora in chronically infected individuals. Consequently, the therapeutic approach involves the escalation of broad-spectrum antibiotic therapy owing to the refractoriness of the infectious clinical condition to drugs.

Furthermore, during hospitalization of all patients, empirical antibiotic therapy with sensitivity profiles directed at more resistant pathogens was introduced without direct identification. It is unclear whether non-targeted therapy to a specific pathogen determines a favorable or unfavorable resolution, but it indicates a pattern of recurrent infections based on the number of readmissions or progression to death, which occurred in one case (D).

Discussion

The analysis of clinical and laboratory data from the selected patients in the context of their respiratory condition raised important points for discussion.

The limited number of patients with both clinical entities as the subjects of the study was initially a reflection of the intersection of two clinical conditions as cause and consequence: sepsis/septic shock and PARDS in patients with chronic diseases.

The recent Phoenix criteria for sepsis and septic shock were developed to expand the diagnosis of these conditions in patients admitted to services with varying levels of resources, compared with the previously used IPSCC criteria, and have been validated in large multicenter studies [18, 10]. These criteria have proven useful in identifying patients with the clinical entities studied, adequately distinguishing them, and correlating them with the clinical conditions presented by the patients in the current case series. This was evident in that in more severely ill patients; intensive escalation of antibiotic therapy was implemented due to the rapid deterioration of their condition.

Given that the Phoenix score includes more specific tests that were not routinely requested during the time frame analyzed, and in the presence of other sepsis criteria, fibrinogen and D-dimer measurements were not requested at the time of diagnosis. Moreover, as the publication date is 2024, studies on the applicability of this score are still lacking.

This characteristic had already been reported in a study conducted by Long et al. [22], which validated the aforementioned score in a multicenter meta-analysis on the epidemiology of sepsis in populations from 2021 to 2023. In that study, a major limitation identified was the lack of complete data for full score application, particularly regarding coagulation parameters—a limitation also observed in the analysis of our population. In Long's study, missing variables were assumed to be within normal ranges, thus avoiding impact on the final score results. Furthermore, as highlighted in that study, the absence of certain biochemical analyses may limit the applicability of the Phoenix score in low- and middle-income settings.

In another recently published study by Sanchez-Pinto et al. [23], a meta-analysis evaluated the validation of the Phoenix score in a multicenter cohort of chronically ill pediatric patients between 2012 and 2018. Including a population of 11,168 patients with confirmed sepsis diagnoses based on the score—approximately 60.8% of whom had comorbidities such as malignancies and transplant status—the study validated the use of the Phoenix score in multi-comorbid patients, finding similar outcomes when compared to previously healthy populations. This conclusion supports the use of the Phoenix score in the present case series, given the similarity between our patient population and that analyzed in the referenced study.

In this regard, the literature supports the applicability of the score in severely ill, multi-comorbid patients—a profile that characterizes the population in our unit—and the results obtained from the score show correlation with the clinical outcomes predicted by the score, despite the presence of missing variables, as observed in our descriptive analysis.

The classification of severity in pediatric acute respiratory distress syndrome (ARDS) has been the subject of studies aimed at better characterizing the impairment of respiratory function in affected patients and directing specific therapies for each severity group, with the goal of improving prognostic outcomes such as days free from mechanical ventilation, length of stay, and mortality. In this context, the Berlin criteria, initially, and PALICC-2, more recently, proposed severity assessment parameters primarily based on the PaO2/FiO2 ratio and oxygenation index (OI) 24 h after the initial insult [9].

Following the publication of these two criteria, several studies have been conducted to evaluate their applicability and to distinguish severity parameters in various intensive care centers. Studies such as Yehya et al. [14], 2015, emphasize that both parameters accurately stratify outcomes related to morbidity and mortality, such as a higher number of days free from mechanical ventilation and its duration in patients who survived by the end of the study. Additionally, they established a timeframe for assessing these two parameters, which was 24 h in the referenced study, while another study by the same author (Yehya et al., 13), 2018, found similar results when evaluated at 6 and 12 h after the insult.

Both of the aforementioned consensus guidelines established the PaO2/FiO2 ratio and oxygenation index (OI) as the standard parameters for assessing severity, being the most accurate for this purpose. Over time,

following their respective publications, various studies have validated that both are consistent in identifying patients with severe ARDS, advocating that when combined with general prognostic factors, the oxygenation index is more accurate in severe cases. In contrast, in patients with mild or moderate disease, the PaO2/FiO2 ratio can be used more easily and quickly because of its simple calculation [12].

As shown in Table 1, the primary parameter for severity assessment was the PaO2/FiO2 ratio, with the oxygenation index being impossible to calculate due to the lack of the "mean airway pressure" parameter provided by the device.

Thus, the main parameter used for stratifying severity during the patients' hospitalization was oxygen saturation measured by pulse oximetry (SatO2) and its SatO2/FiO2 ratio, as shown in Table 3, owing to its ease of measurement. After reviewing the literature, several studies, such as those by Lobete et al. [17] and Khemani et al. [16], have validated the use of this parameter as a noninvasive marker for identifying hypoxemic acute respiratory failure and PARDS.

When compared with the PaO2/FiO2 ratio, the SatO2/FiO2 ratio proved to be appropriate for children with respiratory failure presenting with SatO2 values between 80 and 97%, as all patients in the present study showed [15]. The SatO2/FiO2 ratio and oxygen saturation index (OSI), calculated using the same parameters but in patients on mechanical ventilation, are further supported as methods for discriminating mortality from PARDS in intensive care units, similar to the PaO2/FiO2 ratio and oxygenation index. These parameters are also used for risk stratification and severity scoring, as advocated by Khemani et al. [11] in 2015 and validated in the most recent PALICC criteria [9].

In the analyzed sample, patients exhibited heterogeneity in their underlying clinical conditions. Despite this, all conditions were clinically controlled and unrelated to the acute infectious presentation.

However, the presence of one or, in some cases, multiple chronic diseases are considered strong risk factors for the development of sepsis and septic shock. According to a study by Prout et al. [20], approximately two out of three children admitted to hospitals with a diagnosis of sepsis had at least one chronic condition, a correlation associated with higher in-hospital mortality. In the same retrospective cohort study, the average in-hospital mortality rate was 3.7%, with 0.7% for patients without any underlying conditions, and 5.1% for those with chronic diseases. Furthermore, this study identified that oncological, hematological, metabolic, neurological, cardiac, and renal conditions as well as solid organ transplantation were associated with higher mortality in this patient subset.

Similarly, regarding acute respiratory distress syndrome (ARDS), the study by Nattachai et al. [21] assessed the severity of sepsis at diagnosis and mortality outcomes at 7 and 30 days. The results indicated that higher PIM 3 scores, underlying oncological and hematological conditions, and lower prediagnosis albumin levels were associated with moderate and severe disease at the time of diagnosis. Additionally, patients with oncological and hematological conditions, as well as lower hemoglobin levels due to other underlying diseases, were associated with worse 7-day prognostic outcomes.

Thus, the association between disease severity and the presence of underlying chronic conditions in patients with sepsis or septic shock, as well as PARDS, is well established in the literature and was similarly observed in this case series [20,21].

Another common characteristic among the patients in the current study was the difficulty in conducting an etiological investigation, owing to comorbidities. This challenge arose primarily because these patients exhibited microbial flora with distinct patterns of microorganisms and resistance profiles, resulting in negative serial cultures and necessitating empirical escalation to broad-spectrum antibiotic therapy, including drugs targeting the resistance profiles of nosocomial pathogens.

Despite this chronic and distinct microbial colonization profile in patients with various comorbidities, studies such as that by Phung et al. [19], which evaluated prognostic outcomes related to ARDS in patients undergoing pathogen screening, concluded that no statistically significant differences were observed in the outcomes between the surviving and non-surviving groups. These findings occurred despite differences in the identified pathogens, the incidence of multiple viral infections, sex, age, clinical characteristics, and treatment.

Thus, as observed in this study, the application of two severity scales (PALICC and Phoenix) facilitates the diagnosis, even in milder cases, of chronically ill patients presenting both acute conditions. This sample size could serve as the basis for large-scale studies.

Advantages and Limitations

This study demonstrated the applicability of the PALICC and Phoenix severity scores in chronically ill children and adolescents in the PICU of a tertiary and university hospital, mostly occupied by patients with exacerbated chronic diseases.

Therefore, the use of both scores is essential for the suspicion and diagnosis of such high-mortality conditions.

It is noteworthy that the application of the scores proved to be fundamental, as this is an ICU in a middle-income country, which sometimes has limited resources for diagnosing certain conditions using advanced medical technologies. In this case, a retrospective diagnosis was made using both the scores.

As for limitations, this study was a descriptive case series, focusing on the applicability of the most recent severity scores for PARDS and sepsis in a pediatric population with chronic diseases. Although the sample consisted of only five patients, due to the combined incidence of both diseases being relatively low, mainly in patients with an underlying chronic condition, the study serves as an example of what may occur in larger-scale studies involving a similar patient population, including low and middle-income countries.

The methodological limitation of this study arises from two main sources of potential bias. First, the collection of data for both PALLICC-2 and Phoenix scores - specifically, the ordering of diagnostic tests and the measurement of parameters - was dependent on the individual healthcare professional who provided initial care, this introduces a risk of inter-rater variability, as clinical practice and documentation may differ among clinicians. Second, the selection of pertinent results from the medical records was limited to the researcher who accessed available information at the time. This researcher-dependent selection may introduce a risk of observer bias. However, given the descriptive nature of this case series, the information collected and selected was sufficient for analyzing these parameters within clinical context of the cases presented.

Conclusion

A correlation was observed between the clinical characteristics of the patients and the severity score values. Chronic clinical conditions, such as those presented by the selected patients, may interfere with the etiological identification of the acute septic condition, representing a factor for poorer prognosis, as supported by the literature.

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