Incidence and epidemiology of pediatric acute respiratory distress syndrome in Argentina: Secondary analysis of data from the International PARDIE Study

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ABSTRACT

Introduction. Pediatric acute respiratory distress syndrome (PARDS) poses a clinical challenge due to its high morbidity and mortality. Specific diagnostic criteria exist for the pediatric population; however, evidence in our setting is limited. The objective of this study was to describe the incidence and characteristics of patients with PARDS admitted to Argentine pediatric intensive care units (PICUs) included in the PARDIE multicenter observational study, and to evaluate the factors associated with clinical outcomes.

Population and methods. Secondary analysis of patients enrolled in Argentine pediatric intensive care units for the PARDIE study.

Results. The incidence of PARDS in Argentina was 3.3% (61/1831) among patients admitted to the pediatric intensive care unit (PICU) and 5.1% (61/1203) among those who required mechanical ventilation. Of the 61 patients identified with PARDS, 43 had complete data for the outcome analysis. Mortality in this subgroup was 32.6% (14/43), significantly higher than in the other participating countries (16.1% [107/665]; p <0.01). Argentine patients presented with greater severity at admission, as evidenced by higher PIM3 and vasoactive-inotropic score (VIS) (p < 0.01). At the time of diagnosis of PARDS patients had higher values for tidal volume, peak inspiratory pressure, and FiO_2 (p <0.01). In the exploratory multivariate analysis, mortality was associated with admission to Argentine PICUs and higher severity of PARDS, PIM3, VIS, and immunosuppression.

Conclusion. The incidence of PARDS was higher than in previous epidemiological studies. The higher mortality rate in Argentine PICUs could be related to multiple factors, including severity at admission and a higher incidence of immunosuppression.

Keywords: *acute respiratory distress syndrome; acute hypoxemic respiratory failure; child; pediatric intensive care units.*

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INTRODUCTION

Pediatric acute respiratory distress syndrome (PARDS) poses a significant challenge in intensive care due to its high morbidity and mortality rates.[1,2] In 2015, the first Pediatric Acute Lung Injury Consensus Conference (PALICC-1) was held,[3] during which the pathophysiological, diagnostic, and therapeutic characteristics of pediatric patients were analyzed, and the first specific definition of PARDS was proposed.[4] These recommendations were subsequently updated and expanded at a second consensus conference (PALICC-2).[5]

Based on the PARDS definition, various observational studies have identified regional differences associated with resource availability that may influence clinical outcomes.[4,6,7] In this context, the implementation of protective ventilation strategies during invasive mechanical ventilation (IMV) has been associated with better clinical outcomes, regardless of region.[8-14]

The largest multicenter pediatric epidemiological study published to date is the PARDIE study, which included 145 pediatric intensive care units (PICUs) from 27 countries with varying socioeconomic levels and found a higher risk of adverse outcomes in low- and middle-income countries, including Argentina.[4] Fourteen Argentine PICUs participated in this study, constituting one of the largest national contributions to the international cohort. Information regarding the clinical characteristics and outcomes of PARDS in Argentina is limited. In this context, the objective of this study was to describe the incidence and characteristics of patients with PARDS admitted to Argentine PICUs included in the PARDIE multicenter observational study, and to evaluate the factors associated with clinical outcomes.

POPULATION AND METHODS

Study design and participants

In this secondary analysis of data from the PARDIE study,[4] we analyzed the subgroup of patients recruited by PICUs in Argentina. We compared them with patients from the other participating units. The PARDIE study was an observational, cross-sectional, international, and prospective study. It included children with a new diagnosis of PARDS according to the PALICC-1 definition (*Supplementary material*). At each center, all patients admitted to PICUs were evaluated for inclusion during 5 consecutive-day periods spread over the 10-week study period: every 2 months in 2016 and monthly in 2017.

The incidence was calculated based on the daily screening form, and, in accordance with protocol, only those patients with sufficient information to confirm the diagnosis of PARDS, classify their initial severity, and document the outcome in the PICU were included in the final database used for the analysis of outcomes, including mortality.[4]

The PARDIE study conducted one primary epidemiological study[4] and four secondary studies[6,7,15,16] which included: analysis of ventilatory strategy, evaluation of the sensitivity and specificity of radiographic criteria, evaluation of non-ventilatory support measures, and analysis of outcomes in the group classified as at risk for PARDS. The inclusion and exclusion criteria are detailed in the *Supplementary material*.

The PARDIE study received ethical approval from the participating institutional review boards; full details regarding ethical considerations are provided in the *Supplementary material*.

Data collection

The data were extracted from the PARDIE study database and grouped by admission source: Argentine PICUs and the rest of the world. The following key variables were included in the analysis (see the *Supplementary Material* for the complete list): PICU characteristics, demographic data, severity at admission (Pediatric Index of Mortality [PIM3] and Pediatric Risk of Mortality [PRISM3], associated organ failure [Pediatric Logistic Organ Dysfunction, PELOD], and vasoactive-inotropic score [VIS]).

Variables associated with PARDS: risk factors, severity assessment using the oxygenation index (OI) or oxygenation-saturation index (OSI), chest X-rays, arterial blood gas analysis (pH, arterial carbon dioxide pressure [$PaCO_2$]), arterial oxygen pressure (PaO_2), and pulse oximetry. Duration of support ventilation (invasive mechanical ventilation [IMV] and noninvasive mechanical ventilation [NIV]) causes of death, and clinical outcomes, such as days free of IMV, days free of total ventilatory support (IMV and NIV), and mortality. Data collection of the PARDIE trial focused on the first 72 hours following the diagnosis of PARDS; it then assessed the duration of ventilatory support and mortality in the PICUs or at 90 days, whichever came first.

Statistical analysis

The statistical analysis followed the guidelines

detailed in the main PARDIE study.[4] Continuous variables were described as the median and interquartile range (IQR), and comparisons were analyzed using the Mann-Whitney test. Categorical data were reported as absolute numbers and proportions, and were analyzed using chi-square tests or Fisher's exact test, as appropriate.

As an exploratory analysis, multivariate logistic regression models (with PICU as a random effect) were fitted using variables related to PARDS and mortality. Initially, variables with a univariate association with mortality (p <0.1) were selected, and those that remained associated in the multivariate analysis (p <0.05) or served as confounding factors (OR variation >20%, regardless of the p-value) were retained in the final model. For continuous variables, multicollinearity was assessed using a correlation matrix, and the variable with the strongest univariate association was retained in the final model. A significant p-value was <0.05. The analyses were performed using SAS version 9.4 and STATA™ version 15.

RESULTS

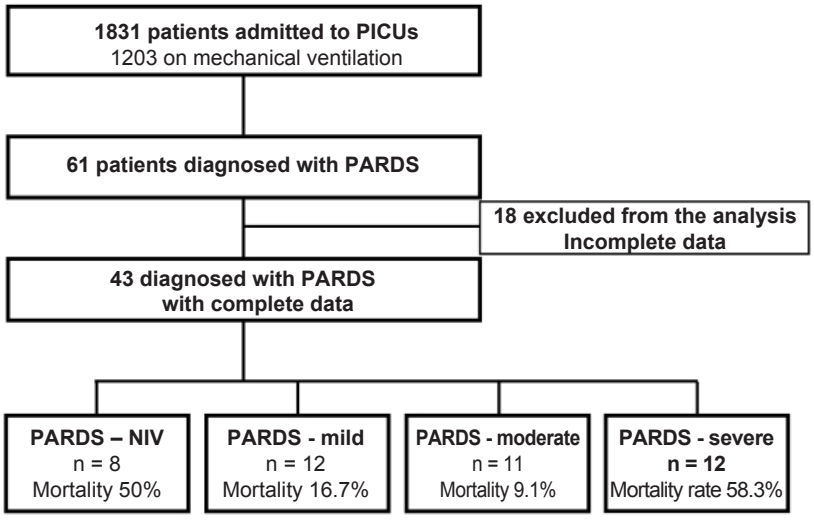
During the 10-week PARDIE study, 23 280 patients were admitted to participating PICUs, and 12 242 (52.6%) required ventilatory support. Among patients admitted to Argentine PICUs, 61 of 1831 (3.3%) met the diagnostic criteria for PARDS, and 61 of 1203 (5.1%) who required VMI did so (*Figure 1*). This proportion was similar to that observed across all participating countries (PICU admissions: 3.2% [3.0-3.4], mechanical ventilation: 6.1% [5.7-6.5]).

Among the patients recruited in Argentina, 43 had complete data for the analysis. The observed mortality rate was 32.6% (14/43), higher than that reported in the other countries, which was 16.1% (107/665) (p <0.01). When stratified by initial severity of PARDS, the distribution among patients on NIV and IMV was similar (*Table 1*). However, mortality in Argentina was higher in the NIV and severe PARDS subgroups. Additionally, patients in Argentina had fewer IMV-free days (*Table 1*).

Regarding PICU characteristics, those in Argentina had lower availability of blood gas analyzers within the unit (67.4% versus 81.4%, p <0.01). However, when classifying the PARDS, a higher rate of use was observed for arterial PaO_2 (88.4% vs. 41.2%; p <0.01), with less use of noninvasive oxygenation indices. The availability of extracorporeal membrane oxygenation (ECMO) in Argentine PICUs was 6.9%, compared with 74.4% reported in other units (p <0.01) (*Supplementary Table 1*).

Patients recruited in Argentina presented with greater severity at admission, as evidenced by higher PIM3-predicted mortality (5.6 [3.6–7.9] vs. 3.1 [0.6–6.5]; p <0.001) and higher initial VIS scores (p <0.01) (*Table 1*). Risk factors were similar, with pneumonia (30/43; 69.8%) and sepsis (12/43; 27.9%) being the most

Figure 1. Patient flowchart. Argentine pediatric intensive care units



PICUs: pediatric intensive care units, PARDS: pediatric acute respiratory distress syndrome, NIV: noninvasive ventilation.

Table 1. Characteristics and outcomes of patients with pediatric acute respiratory distress syndrome*

Variable	Argentina n = 43[1]	Rest of the world n = 665[1]	*p*-value
Demographic characteristics			
Weight (kg)	12 (7.5-16.0)	15 (8.0-32.7)	0.06
Height (cm)	84 (64-110)	92.5 (68-129.5)	0.13
Female	21 (48.8)	253 (38.1)	0.12
Age (months)	1.9 (0.7-5.3)	3.6 (0.7-10.5)	**0.02**
PIM 3 (%)	5.6 (3.6-7.9)	3.1 (0.6-6.5)	**<0.01**
PRISM 3 (%)	4.9 (2.5-8.7)	3.4 (1.6-10.3)	0.10
PELOD Day 0	2 (2-3)	2 (1-4)	0.60
Initial VIS	10 (0-30)	0 (0-10)	**<0.01**
Severity of PARDS			0.79
NIV	8 (18.6)	153 (23.0)	
Mild	12 (27.9)	209 (31.4)	
Moderate	11 (25.6)	143 (21.5)	
Severe	12 (27.9)	160 (24.1)	
PARDS diagnosis			
OI (OSI converted to OI, VMI only)	10.1 (6.5-19,3)	10,0 (6,0-19,6)	0,90
Classification based on arterial pO_2	38 (88.4)	274 (41.2)	**<0.01**
Bilateral infiltrates	38 (88.4)	485 (72.9)	0.08
Comorbidities			
No comorbidities	23 (53.5)	422 (63.5)	0.19
Left ventricular dysfunction	5 (11.6)	35 (5.3)	0.08
Prematurity	5 (11.6)	126 (18.9)	0.23
Chronic lung disease	7 (16.3)	190 (28.6)	0.08
Congenital heart disease	3 (6.9)	75 (11.3)	0.38
Acquired heart disease	0 (0)	56 (8.4)	0.05
Neuromuscular disease	3 (6.9)	119 (17.9)	0.07
Cancer	7 (16.3)	52 (7.8)	0.05
Non-cancer-related immunosuppression	5 (11.6)	90 (13.5)	0.70
Chronic ventilatory support	1 (2.3)	119 (17.9)	**0.01**
Risk factors for PARDS			
Pneumonia	30 (69.8)	415 (62.4)	0.33
Sepsis	12 (27.9)	124 (18.7)	0.14
Aspiration	0 (0)	60 (9.0)	**0.04**
Outcomes			
PICU mortality	14 (32.6)	107 (16.1)	**<0.01**
90-day mortality	14 (32.6)	122 (18.4)	**0.02**
IMV-free days	15.3 (0-21.1)	20.7 (7.4-24.6)	**<0.01**
IMV and NVI-free days	14.9 (0-20.3)	13.1 (2.1-23.5)	**0.01**
Duration of IMV ventilation (days) (survivors)	9.2 (5.5-13.1)	7.4 (4.3-12.9)	0.19
Duration of NIV (days) (survivors)	0.6 (0.2-4.8)	1.4 (0.3-4.2)	0.46

** Analysis of patients with complete clinical outcome data (n = 43).*

[1] Median (interquartile range); n (%).

PIM 3: Pediatric Index of Mortality 3, PRISM: Pediatric Risk of Mortality, PELOD: Logistic Organ Dysfunction, PARDS: pediatric acute respiratory distress syndrome, OI: oxygenation index, OSI: oxygenation-saturation index, VIS: vasopressor-inotropic score index, NIV: noninvasive ventilation, IMV: invasive mechanical ventilation, PaO_2: arterial oxygen pressure, PICU: pediatric intensive care unit.

common. However, aspiration was less frequent in Argentina (p = 0.04). Regarding comorbidities, trends toward higher proportions of patients with cancer were observed in Argentina (7/43 [16.3%] vs. 52/665 [7.8%]; p = 0.05) and left ventricular dysfunction at admission (5/43 [11.6%] vs. 35/665 [5.3%]; p = 0.08) (*Table 1*).

In the analysis of ventilatory management on Day 0 of the PARDS, significant differences were found in the following variables: Argentine

patients received higher expiratory tidal volumes (VTe/kg of body weight) (8.1 [7-8.5] vs. 6.6 [5.8-7.8] mL/kg, *p* <0.01), and higher levels of inspiratory pressure peak inspiratory pressure (PIP) (30 cmH_2O [28-34] vs. 26 [22-30], *p* <0.01) with a higher inspired oxygen fraction (FiO_2) (0.6 [0.6-0.8] vs. 0.5 [0.4-0.6], *p* <0.01).

No differences were observed in positive end-expiratory pressure (PEEP) levels or in the PaO_2 and $PaCO_2$ values (*Table 2*).

Regarding non-ventilatory therapeutic support, Argentine patients showed greater use of prone positioning (*p* <0.01) and less use of neuromuscular blockers (NMBs) administered by continuous infusion (*p* <0.01), but no differences in overall use (*p* = 0.12). No differences were observed in the use of complementary therapies, including inhaled nitric oxide (iNO) and ECMO (*Supplementary Table 2*).

A higher proportion of deaths in Argentina were due to multiple organ failure, refractory hypoxemia, and shock, with no reported deaths from neurological causes (*Supplementary Table 3*). In the exploratory multivariate analysis, after adjusting for the severity of PARDS, PIM3, initial VIS score, and history of immunosuppression, an association was observed between admission to an Argentine PICU and higher mortality (OR 2.84 [1.20-6.73]) (*Table 3*).

DISCUSSION

In this study, the incidence of PARDS in ventilated patients in Argentina, based on the PALICC-1 criteria, was 5.1%, higher than that reported in previous epidemiological studies (2% and 3%),[17,18] which used the American-European Consensus definition.[19] This higher incidence correlates with the results of the PARDIE study, in which the PALICC-1 definition identified 40% more children with PARDS compared to the Berlin definition.[4] Although the availability of blood gas analyzers within PICUs was lower in Argentina, at the time of diagnosing and categorizing PARDS, it was observed that greater use of arterial PaO_2, with lower use of noninvasive oxygenation indices, was observed. This may reflect differences in monitoring patterns and local clinical practices, unrelated to equipment availability.

We observed that the mortality rate among patients with PARDS admitted to Argentine PICUs was significantly higher than that observed in other countries: 32.6% vs. 16.1%. Furthermore, there has been a progressive decline in mortality rates reported in previous studies: 50% in 2004,[17] 39% in 2012,[18] and 32.6% in the present study, with comparable stratification of PARDS severity (PALICC-1) at the time of diagnosis among the units participating in the PARDIE study.

The PARDS-NIV mortality rate reported in the secondary analysis of the PARDIE study was 15%,[20] whereas the rate observed in our units was 50%. Although mortality was higher in the PARDS-NIV group, no independent association was observed in the multivariate analysis. About NIV, a delay in transitioning to MIV is associated with worse outcomes; therefore, adherence to the current PALICC-2 recommendations is

Table 2. Ventilatory parameters on day 0 of pediatric acute respiratory distress syndrome

Variable	Argentina n = 43[1]	Rest of the world n = 665[1]	*p*-value
VTe (mL/kg)	8.1 (7-8.5)	6.6 (5.8-7.8)	**<0.01**
FiO_2 (%)	0.6 (0.6-0.8)	0.5 (0.4-0.6)	**<0.01**
PIP (cmH_2O)	30 (28-34)	26 (22-30)	**<0.01**
PEEP (cmH_2O)	8 (6-10)	8 (6-10)	0.76
MAP (cmH_2O)	14 (12-19)	14 (12-17)	1
RR	22 (20-25)	24 (18-30)	0.32
pH	7.32 (7.26-7.37)	7.34 (7.28-7.40)	0.17
$PaCO_2$ (mmHg)	45 (37-57)	46.5 (40-56)	0.72
PaO_2 (mmHg)	90 (76-133)	85 (71-98)	0.06

** Analysis of patients with complete clinical outcome data (n = 43).*

[1] Median (interquartile range).

VTe: tidal volume/expiratory flow; kg: kilograms, FiO_2: inspired oxygen fraction, PIP: peak inspiratory pressure, PEEP: positive end-expiratory pressure, MAP: mean airway pressure, RR: respiratory rate, $PaCO_2$: partial pressure of CO_2, PaO_2: partial pressure of O_2.

essential at implementation.[5] Regarding the characteristics of patients admitted to Argentine PICUs, several variables associated with mortality were identified. Among these, a higher proportion of immunosuppressed patients was observed, a factor previously described as associated with mortality in PARDS.[4,6] This higher incidence could be related to the number of participating units belonging to pediatric referral centers. Other factors associated with mortality included indicators of greater severity at admission, such as higher PIM3 and VIS vasopressor scores. This greater severity at admission is consistent with findings from the PIM3 validation study in Argentina and may reflect reduced access to PICUs in our country.[21] While these associations do not necessarily imply causality, they could point to opportunities for improvement, particularly in the early identification of at-risk patients with access to timely admission to the intensive care unit.

Although these variables may partially explain the observed mortality, it remained high in Argentina even after adjusting for these factors, suggesting the existence of other determinants. In this study, we observed that in Argentine PICUs, at the time of PARDS diagnosis, Vte/kg values were higher at similar PEEP levels and higher FiO_2.

A secondary analysis of the PARDIE study reported increased mortality among patients who did not adhere to the Vte/kg recommendations and whose PEEP settings were below the values recommended by the ARDSnet PEEP/FiO_2 table.[7] Quality improvement studies that implemented protective ventilation protocols—including adjusting VTe/kg based on severity and setting PEEP according to ARDSnet tables (lower levels)—have reported a reduction in mortality.[8,9] In the PARDIE study, plateau pressure could not be analyzed because it was recorded in only 2.9% of patients, which also prevented the evaluation of driving pressure.[7]

Regarding complementary therapeutic strategies, the use of prone positioning was similar to that reported in South America and slightly higher than in Europe.[22] However, since it was not included in the multivariate analysis, it was not possible to determine its impact on outcomes. The use of ECMO and continuous neuromuscular blockade was comparable to that described in low- and middle-income countries, consistent with our healthcare context.[22]

One of the main limitations of this study is the exclusion of nearly 30% of patients, which could introduce selection bias. The exclusion of patients with incomplete data may also have affected the estimate of observed mortality; therefore, these results should be interpreted with caution. Furthermore, the small number of included subjects precluded a stratified analysis by PARDS severity and, consequently, a detailed assessment of the impact of adjuvant therapies (such as ECMO and prone positioning) on morbidity and mortality. The multivariate analysis included 43 patients with PARDS and 14 mortality events; this ratio may compromise the stability of the estimates and account for the width of the confidence intervals. In this context, given the exploratory nature of the multivariate analysis, the results should be interpreted with caution and not used to establish causal associations. Despite these limitations, the clinical findings—though unfavorable relative to the indicators—point to opportunities to align protocols with international guidelines and to optimize the management of patients with PARDS.

CONCLUSION

The higher observed incidence of PARDS is consistent with findings from the PARDIE study, which reported a higher detection rate among patients who met the PALICC definition. The association with higher mortality in Argentine PICUs could be related to multiple factors, including severity at admission and a higher incidence of immunosuppression. ■

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The supplementary material provided with this article is presented as submitted by the authors. It is available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2026/10987_AO_Herrera_Anexo.pdf

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