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Immunocompromised-associated Pediatric Acute Respiratory Distress Syndrome: Experience from the 2016/2017 Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology Prospective Cohort Study

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Tweet: Immunocompromised-associated PARDS **(**I-PARDS) is a unique subtype of PARDS associated with hospitalization prior to diagnosis, increased time in at-risk for PARDS, utilization of more NIV, increased hypoxia, more non-pulmonary organ dysfunction, and increased mortality.

The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Abstract

Objective: To characterize immunocompromised-associated PARDS (I-PARDS) and contrast it to PARDS

Design: This is a secondary analysis of the 2016–2017 PARDS incidence and epidemiology (PARDIE) study, a prospective observational, cross-sectional study of children with PARDS

Setting: Dataset of 145 Pediatric Intensive Care Units (PICUs) across 27 countries

Patients: During 10 non-consecutive weeks (from 5/2016–6/2017), data about immunocompromising conditions (ICC, defined as malignancy, congenital/acquired immunodeficiency, post-transplantation, or diseases requiring immunosuppression) were collected.

Interventions: None

Measurements and main results: Of 708 subjects, 105 (14.8%) had ICC. Prior to the development of I-PARDS those with ICC were more likely to be hospitalized (70% vs 35%, p <0.001), have more at-risk for PARDS (p=0.046), and spent more hours at-risk (20 [IQR:8–46] vs 11 [IQR:4–33], [p=0.002]). NIV use was more common in those with ICC (p<0.001). Of those diagnosed with PARDS on NIV (n=161), children with ICC were more likely to be subsequently intubated (n=28/40 [70%] vs n=53/121 [44%], p=0.004). Severe PARDS was more common (32% vs 23%, p<0.001) in I-PARDS. Oxygenation indices were higher at diagnosis and had less improvement over the first 3 days of PARDS (p<0.001). Children with I-PARDS had greater nonpulmonary organ dysfunction. Adjusting for PRISM IV and oxygenation index, children with I-PARDS had a higher severity of illness-adjusted PICU mortality (aHR:3.0 [95% CI:1.9, 4.7] p<0.001) and were less likely to be extubated alive within 28 days (sHR: 0.47 [95% CI:0.31, 0.71] p<0.001).

Conclusions: I-PARDS is a unique subtype of PARDS associated with hospitalization prior to diagnosis and increased: time at-risk for PARDS, NIV use, hypoxia, non-pulmonary organ dysfunction, and mortality. The opportunity for early detection and intervention seem to exist. Dedicated study in these patients is imperative to determine if targeted interventions will benefit these unique patients with the ultimate goal of improving outcomes.

Keywords

Immunocompromised Host; Respiratory distress syndrome; respiratory insufficiency; pediatrics; pediatric intensive care unit

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One of the more challenging diagnoses in pediatric critical care is pediatric acute respiratory distress syndrome (PARDS). In the original report of the PARDS Incidence and Epidemiology (PARDIE) study we found PARDS occurs in 2–4% of patients admitted to the PICU, has a mortality rate of 20%, and has no specific treatment beyond optimizing

supportive care(1). In a subsequent publication using the PARDIE dataset and an external validation cohort immunocompromised children were found to have seven times the odds of mortality (2). Previous work in the most severely immunocompromised, those post hematopoietic cell transplant (HCT) show a high risk of PARDS at intubation and suggest that earlier interventions may attenuate poor outcomes(3, 4). Data about at-risk for PARDS, first proposed by the Pediatric Acute Lung Injury Consensus Conference (PALICC) (5) and further described by the PARDIE study, (6, 7) shows worse outcomes for all children who progress to PARDS from at-risk for PARDS. Additionally, data from PARDIE has recently shown that immunosuppression amongst other factors are independently associated with NIV failure (defined as intubation or death). NIV failure was 100% among patients with nonrespiratory PELOD-2 score greater than 2, Pa_{O_2}/F_{IO_2} less than 100, and immunosuppression all present(8). As the previous works from the PARDIE dataset have demonstrated ICC to have increased risks we embarked on this study to further describe this vulnerable population.

Since ICC with PARDS is associated with greater odds of mortality and NIV failure, in this report we aimed to better characterize the differences between PARDIE groups with and without ICC. We hypothesize that PARDS in children with ICC is fundamentally different from severe PARDS. We call this entity I-PARDS: Immunocompromised-associated Pediatric Acute Respiratory Distress Syndrome.

Materials and Methods:

Study design and patient selection

This is a secondary analysis of the PARDIE study. This large, international, cross-sectional study of PARDS was completed in 2016–2017, and the methodology and findings have been described in several reports (1, 2, 8). In brief, sites received regulatory/ethical approval locally or relied on the Children's Hospital of Los Angeles Institutional Review Board (CHLA-16–00043, approved 2/8/16). Consent was waived. Procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation and with the Helsinki Declaration of 1975.

PARDIE prospectively enrolled 708 subjects from 145 PICUs in 27 countries; each site prospectively screened over 5 days during 10 nonconsecutive weeks between May 2016 and June 2017. Patients were included if they met PALICC PARDS criteria (5) within 24 hours of enrollment including clinical insult within the previous 7 days, respiratory failure not fully explained by cardiac failure or fluid overload, new infiltrates on imaging and a hypoxemia minimum. Exclusions included: perioperative status from cardiac intervention and active perinatal lung disease. Demographics, center characteristics, and geographic categorization were collected. Data were collected at study entry and for the first 3 days after PARDS diagnosis, including oxygenation, ventilatory support, radiographs, daily (calendar day) non-pulmonary organ failure (Pediatric Logistic Organ Dysfunction [PELOD] 2 score) (9, 10), vasopressor requirement, fluid balance, use of ancillary therapies and comorbidities. Severity of illness measured using Pediatric Index of Mortality (PIM) 3 (11) and Pediatric Risk of Mortality (PRISM) IV (12) scores were collected at PICU admission. Ventilator data was censored at 28 days. Immunosuppressed status was noted with subtypes of etiologies,

including: malignancy, transplant status (solid organ or HCT), congenital or acquired immunodeficiency, or autoimmune disease on immunosuppressive therapy. Non-pulmonary organ dysfunction was defined as a non-pulmonary organ PELOD-2 score > 0. The following data were used as surrogate markers of organ dysfunction: cardiovascular using vasoactive medications and vasopressor inotropic score (13); renal using fluid balance (mL/kg), diuretic treatment, and renal replacement therapy; hematological using blood product administration; metabolic/nutritional using parenteral nutrition prescription and treatment with insulin. All were collected on PARDS diagnosis and on Days 1, 2 and 3 and evaluated as organ dysfunction at any of these time points vs never having non-pulmonary organ dysfunction during that time. At-risk for PARDS and PARDS stratification were defined using the PALICC definitions (5, 14).

Statistical Analysis

Patients with or without ICC were compared. These results are presented as medians with interquartile ranges (IQRs) for continuous variables and compared using the nonparametric Wilcoxon rank sum test or as frequencies with percentages for categorical variables, and compared using the Chi-square or Fisher exact tests. For variables with more than two categories, pairwise comparisons were also done to obtain individual p values and were adjusted using Bonferroni correction. To control for repeated measures within patients, mixed effects longitudinal analysis with unstructured covariance and an interaction term was used to compare the difference in oxygen saturation index (OSI) changes over time. Cox proportional hazard regression was used to determine ICC association with mortality. Kaplan Meier was used to produce a 90-day mortality survival curve. Duration of ventilation was assessed with a competing risk regression model with successfully extubated and alive at 28 days as the outcome (analogous to ventilator free days at 28 days) and death as the competing risk. Both models were adjusted for PRISM IV score and initial oxygenation index (OI) equivalent (15) (OSI was transformed into an OI equivalent if OI not available). These covariates were chosen a priori to control for severity of PARDS at diagnosis and general risk of mortality. Race was equal between groups likely negating effect of skin tone on oxygenation measures. Models with and without race as a variable yielded the same results (data not shown). The threshold for statistical significance was set at $p<0.05$. STATA, for Windows, Version 17, was used for the analyses.

Results:

There were 708 children in the PARDIE cohort, of whom 14.8% (n=105) had ICC. The most common three ICCs were leukemia (27%), S/P allogeneic HCT (22%) and a congenital or primary immunodeficiency (10%) additional diagnoses are listed in Table S1. Patients with ICC were older ($p< 0.001$) and less likely to have additional comorbidities (Table 1). At PICU admission, on univariable analysis, children with ICC were more likely to be admitted from the ward and have higher PRISM IV scores). There was no difference in sex or geographic region.

PARDS diagnosis

Those with ICC were more likely to meet at-risk for PARDS criteria (p=0.046), which were often met before PICU admission (Table 2). These individuals had longer duration in at-risk for PARDS prior to PARDS development (p=0.002). The majority of the cohort was diagnosed with PARDS in the PICU. Risk factors for PARDS differed between groups. Those with ICC were more likely to have bilateral chest radiograph findings at diagnosis, and over the first two days of PARDS (Table S2). Children with ICC were more likely to be diagnosed with PARDS while on NIV (p<0.001). While children without ICC had a relatively even division of severity of PARDS at diagnosis, those with ICC had a bimodal distribution with the highest proportions being NIV PARDS and severe PARDS.

PARDS severity

Dichotomizing patients into severe versus not severe PARDS, those with ICC had a higher proportion with severe PARDS at diagnosis on all three study days and an overall higher severity of PARDS (Fig 1a and Fig S1). OSI and OI were consistently higher at every 6-hour interval during the 72 hours following PARDS diagnosis (Fig 1b and Fig S2). While OSI in both groups had a general downward trend those with ICC had significantly less improvement in OSI over time (p = 0.001).

Mechanical ventilation and other supportive therapies

NIV was used more in those with ICC (p<0.001). Of those diagnosed with PARDS on NIV (n=161) the presence of ICC was associated with greater odds of subsequently requiring intubation (28/40 [70%] vs 53/121 [44%], p = 0.004; OR=2.99 [95%CI: 1.39 to 6.44], p = 0.005). Children with ICC spent a median of 13.8 (IQR: 3.1 to 34.8) hours on NIV with PARDS prior to intubation. A greater percentage of children with I-PARDS diagnosed on NIV progressed to severe PARDS (37.5% vs 19.8%, p=0.024) (Table S3). Mechanical ventilation strategies differed between groups on all three days with a higher proportion of those with ICC receiving NIV and high frequency oscillatory ventilation on analysis corrected using Bonferroni for multiple comparisons (p<0.001) (Table S4). Despite the higher percentage of severe PARDS in patients with ICC, we did not identify any association with use of pulmonary specific ancillary therapies such as inhaled nitric oxide, continuous neuromuscular blockade, prone positioning or extracorporeal membrane oxygenation (ECMO) (Table S5). More children with ICC received steroids (p<0.001), but not steroids specifically for PARDS (p=0.185).

Organ Dysfunctions and Outcomes

Non-pulmonary organ dysfunction at any point during the study period was more common in those with ICC (Table 3). While cardiovascular dysfunction was not different based on PELOD criteria, those with ICC used more vasoactive medications (p=0.005) and had a higher vasopressor-inotrope score at diagnosis (p=0.001). Renal dysfunction as exemplified by renal PELOD score (p=0.005), use of renal replacement therapy (p<0.001), and diuretic use (p=0.006) was greater in children with ICC. No difference in fluid balance at diagnosis, days 1, 2 or 3, was found (Table S6). Those with ICC had more hematological dysfunction by PELOD criteria (p<0.001) and blood product transfusions on the day of diagnosis and

subsequent three days. Total parenteral nutrition and insulin use were greater in children with ICC (p<0.001).

I-PARDS was associated with worse outcomes (Table 3). PICU mortality was higher in those with I-PARDS compared to PARDS (43.8% [n=46] vs 12.4% [n=75], p<0.001). Those with ICC had significantly lower 90-day survival (Fig S3). Adjusting for initial OI equivalent and PRISM IV score, those with ICC had a higher risk for both PICU (aHR:3.0 [95% CI:1.9, 4.7], p<0.001) and 90-day mortality (aHR:2.9 [95%CI: 1.9, 4,5], p<0.001). A sensitivity analysis replacing PRISM IV with PIM and PELOD yielded similar results (data not shown). Children with ICC were more likely to die with multiorgan failure (p<0.001) and refractory shock (p=0.002). Those with ICC consistently had a higher 90-day mortality regardless of initial severity of PARDS or worst overall severity of PARDS (Fig 1). On subgroup analysis we stratified by severe and non-severe PARDS at diagnosis and worst PARDS overall, those with ICC had an increased risk of mortality in all categories (initial non-severe PARDS, initial severe PARDS, maximum non-severe PARDS, maximum severe PARDS (all p values <0.001) (Table 3). Those with ICC also had fewer median VFD at 28 days (0 [IQR: 0, 22.3] vs 20.9 [11.8, 24.6] days, p<0.001). Adjusting for initial OI and PRISM IV with death as a competing risk, those with ICC had a sub-distribution hazard ratio that indicated they had a 53% reduction in being extubated alive within 28 days (sHR: 0.47 [95% CI:0.31, 0.71] p<0.001). Median PICU length of stay in survivors was not different (12.0 [7.6, 16.4] vs 10.6 [6.4, 19.8] days, p=0.311). While ECMO utilization was not different between groups mortality in those without ICC was 28% (5/18) and in those with ICC was 80% (4/5).

Hematopoietic Cell Transplant Recipients

The number of those post-HCT is small, but as there is special interest in this high-risk group, we have included a parallel analysis of ICC with no allogeneic HCT and those post-allogeneic HCT. Patients post-allogeneic HCT trended towards more severe PARDS, had significantly increased hospital mortality and fewer ventilator free days. (See HCT supplement).

Discussion

The PARDIE 2016–2017 international cohort of patients with PARDS demonstrates important differences in those with ICC. Our investigation suggests that I-PARDS is characterized by the following: more time spent in at-risk for PARDS; more NIV use; greater proportion of mortality occurring across PARDS severity categories; and more non-pulmonary organ dysfunction. ICC was associated with greater hazard of mortality in the PICU and at 90-days. Many of these characteristics have also been noted in adults with ICC and ARDS (16). These observations extend our previous reports of ICC and NIV in the PARDIE dataset (2, 8) and show that I-PARDS deserves its own distinction. Children with I-PARDS have significant ICU needs, and as more ICC patients are hospitalized prior to PARDS diagnosis, they offer a unique opportunity for early and specific interventions.

At-risk for PARDS has worse outcomes when it progresses to PARDS (6). Children with ICC may represent an ideal population for early, targeted interventional trials to change

the trajectory of at-risk for PARDS with the ultimate goal of preventing or attenuating PARDS. Opportunities to study interventions such as early initiation of respiratory support, aggressive diuresis, or novel therapies may be more feasible in this population. We, along with previous studies (17, 18) demonstrated these patients are more likely to be hospitalized prior to PICU admission as compared to the general pediatric population. As children with ICC meet at-risk for PARDS criteria for longer, close monitoring for at-risk for PARDS may be useful in modifying the course and outcomes of I-PARDS.

Given the longer duration of at-risk for PARDS, higher use of NIV and higher rate of subsequent intubation, optimal pre-intubation respiratory support warrants investigation in children with ICC. Early continuous positive airway pressure in children with impaired immunity showed greater odds of mortality when this intervention was used, rather than standard care (19). In a 2009 – 2014 cohort of pediatric HCT recipients with respiratory failure, NIV exposure prior to intubation was associated with a higher PICU mortality (20) and the development of PARDS (21). In a multicenter study of children post-HCT from 2010 – 2016, 60% failed NIV requiring intubation, compared to other general pediatric studies (some of which included ICC patients) showing an NIV failure rate of 18.7%−50% (8, 22, 23). More concerning, there was approximately a 10% cardiac arrest rate with intubation in the post-HCT population (22), which may be attributable to suboptimal timing of intubation. A Virtual PICU Systems Cohort (2014–2019) showed that pre-intubation NIV is associated with increased mortality, but only in children with ICC (17). The explanation for this association is unclear. One possibility described in the LUNG SAFE study of adult ARDS is that increased tidal volumes and transpulmonary pressures that can be injurious to the lung (24). Taking all of the above studies together, similar to adults with ICC (25), these data indicate that children with ICC who are not exposed to NIV prior to intubation have improved survival. We suggest that NIV use in I-PARDS needs a dedicated trial that, at a minimum, should investigate the optimal timing of NIV, as well as identify which patients should forgo a NIV trial and be intubated.

I-PARDS may be distinct from PARDS due to its underlying pathobiology. Since ICC increases the risk of infection, recurrent infections and inflammatory insults could lead to abnormal lung parenchyma, and potentially to more severe PARDS. Additionally, children with ICC are at risk for noninfectious pulmonary complications like graft-versus host disease, idiopathic pulmonary syndrome, bronchiolitis obliterans and other disease states ultimately leading to alveolar destruction (26). Thrombotic microangiography, abnormal endothelium, and pulmonary hemorrhage can contribute to pulmonary vasculature abnormalities and impaired gas diffusion (27). Children with ICC can have a dysregulated immune system which may respond inappropriately when faced with an infection or other inflammatory stressor resulting in the higher rates of non-pulmonary organ dysfunction. For example, phenotype 1 (hypo-inflammatory) and phenotype 2 (hyper-inflammatory) (28, 29) data lend credibility to potential biological differences. The biologic and inflammatory differences may in-part contribute to the higher rates of non-pulmonary organ failure seen in I-PARDS. These differences may open avenues for novel therapeutic pathways specifically in patients with ICC. Defining the difference in clinical presentation of I-PARDS is the first step needed to lay the foundation for future investigations of PARDS in children with ICC.

Our clinical approach to those with ICC may differ from our usual care for PARDS patients. For example, the PARDIE 2016–2017 experience of prolonged time spent in at-risk for PARDS, more NIV use at diagnosis, and the longer time on NIV prior to intubation, may reflect a clinical bias in practice for such patients based on historical outcomes (4) and may impact the treatment strategies employed in I-PARDS. The suggestion of a delay in intubation is reflected in the 2009–2014, twelve-center study of children post-HCT; children on supplemental oxygen for a week before intubation had higher mortality (3). This same cohort had greater odds of mortality for each day spent in the PICU prior to intubation (20). Clearly, we need to better understand the contemporary landscape of possible clinical biases in PICU practice and how they may impact the care of I-PARDS.

Through this study we have found that I-PARDS is distinct from PARDS and deserves its own categorization and dedicated investigation. The access to high level medical care at time of I-PARDS development, the degree and number of organ failures, potential prior medication exposures, particularly those with cardiac and pulmonary toxicities, and the associated high mortality demonstrate an opportunity and urgent need for investigation. As a community, we should not be excluding (30–33) children with ICC from PARDS clinical trials if we hope to change I-PARDS outcomes. While children with ICC constitute a fraction of the PICU population, they are responsible for a large burden of mortality. In this study children with ICC were less than 15% of the total cohort of 708 however, they were responsible for 38% of the mortality.

This study does have limitations. First, as a secondary analysis of a larger 2016–2017 cohort, we do not have detail on the degree or type of immunodeficiency beyond underlying diagnosis. Understanding if the type of immunodeficiency, degree of immunosuppression, and/or prior medication/radiation exposure impacts I-PARDS outcomes is important. Second, diagnosis of organ dysfunction remains challenging in pediatric critical care (34) and medication utilization as a proxy for single organ dysfunction may be misleading. Third, data on degree of oxygenation failure and PARDS supportive strategies were only collected for 3 days following PARDS diagnosis. Data prior to patients having PARDS are limited and there may be therapies employed later in the course of PARDS that were not captured. As this is an observational study, individual clinicians at the beside made decisions when to place on NIV, when to intubate, when to use ancillary therapies, etcetera and there is no standardization globally of these practices. Fourth, As the children with I-PARDS were different in age, illness severity scores, and organ dysfunctions, we may not be comparing like groups which supports the argument that this population needs dedicated study. The large number of patients from multiple different institutions and countries adds strength to this study to help overcome these limitations but we cannot exclude the fact that these data are now 7 years old.

Conclusion

The 2016–2017 PARDIE cohort characterizes I-PARDS in which patients: 1) Are hospitalized prior to a diagnosis of PARDS 2) have increased at-risk for PARDS 3) receive more support with NIV 4) have more severe hypoxia 5) develop more non-pulmonary organ dysfunction and 6) have greater odds of mortality. These patients are in the wards, and we

are providing high-intensity medical care, yet outcomes remain poor. We desperately need to study these patients to improve their outcomes. Future investigation should work to develop targeted, optimized therapies to improve overall outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context:

- Children with immunocompromising conditions are hospitalized prior to PARDS development
- These children have a higher risk of PARDS as compared to their immunocompetent peers
- In the 2016/2017 PARDIE dataset PARDS in immunocompromised children was associated with seven times the mortality as compared to children without immunocompromise

What This Study Means:

- We have a unique opportunity to identify immunocompromised children who are in the category at-risk for PARDS, which may be the ideal time for intervention
- Use of non-invasive ventilation leading to a potential delay in intubation needs further study especially in immunocompromised children
- Outcome measures, including mortality and organ dysfunction, are worse in children with PARDS who have immunocompromising conditions

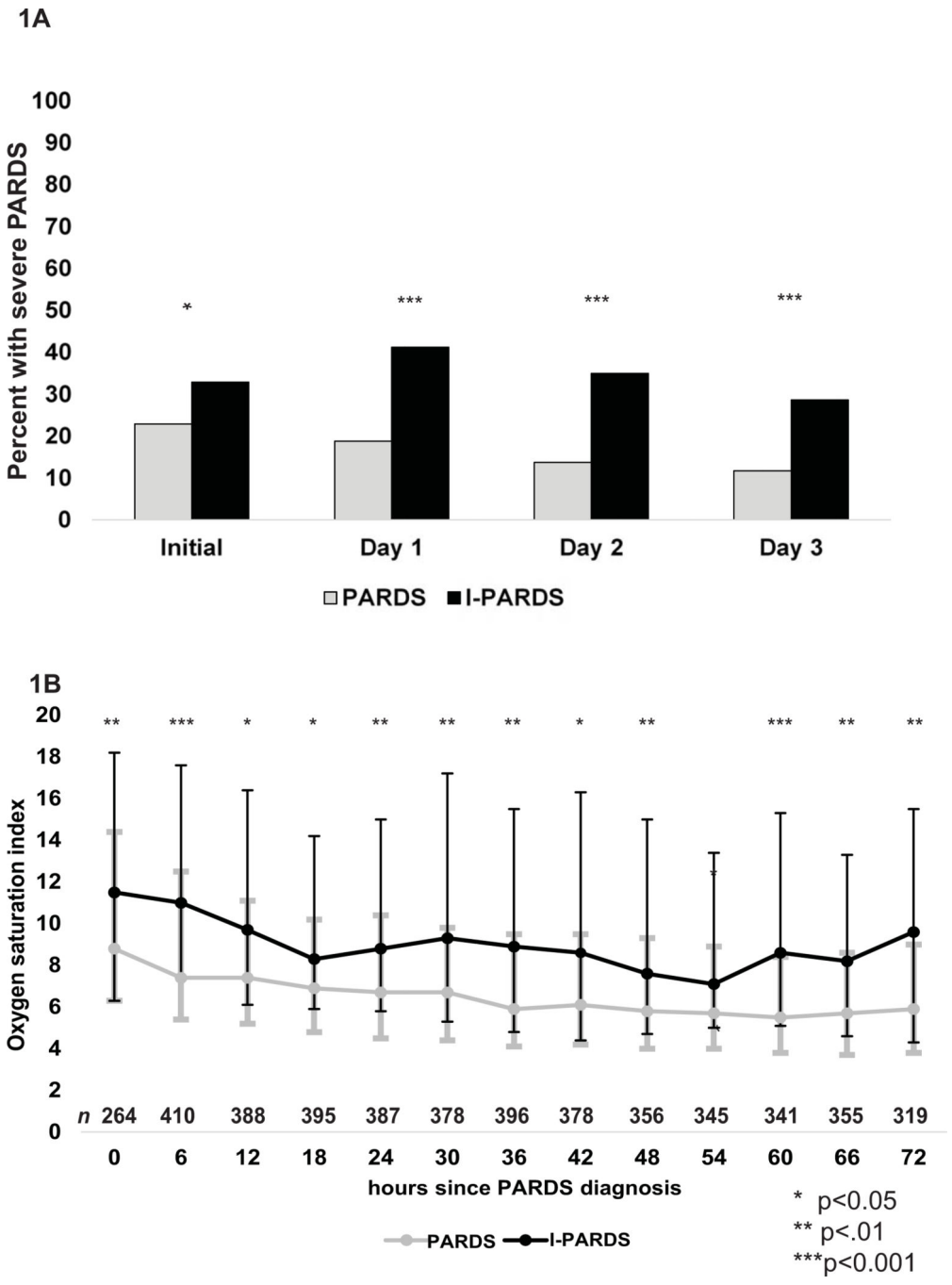

Figure 1:

Figures 1a and b demonstrate the severity of PARDS and oxygenation failure over the first 3 days of PARDS.

Figure 1A: **Percentage of patients with severe PARDS over time stratified by immune status**. The figure shows the difference in percentage of patients comparing those with PARDS (with no immunocompromising conditions ICC) (gray bars) to those with I-PARDS (with ICC) (black bars) at diagnosis, and the first three days of PARDS.

Figure 1B: **Median OSI trends over the 1st three days of PARDS stratified by immune status**. The figure shows trends in the median OSI every six hours over the first three days comparing those with PARDS (with no immunocompromising conditions ICC) (gray line) to those with I-PARDS (with ICC) (black line). Error bars represent the interquartile ranges for each time point. Using mixed effects longitudinal analysis to control for repeated measures within patients, those with I-PARDS had less improvement in OSI over time ($p < 0.001$) *$p<0.05$, **$p<0.01$, ***$p<0.001$

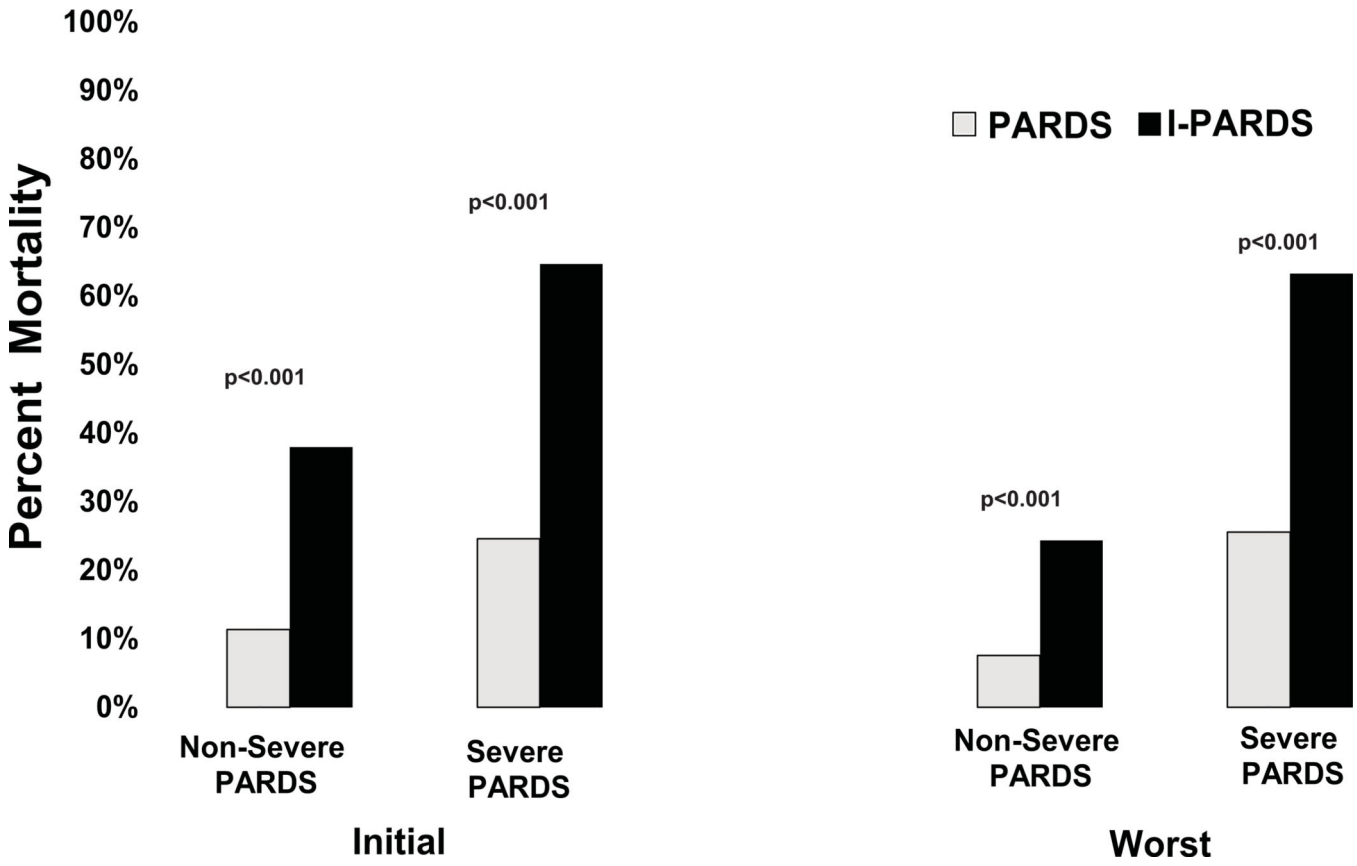

Figure 2: Mortality stratified by PARDS severity.

Figure 2 illustrates mortality differences between those with PARDS (with no immunocompromising conditions ICC) (gray bars) and I-PARDS (with ICC) (black bars) stratified by initial PARDS severity and worst overall PARDS severity.

Table 1:

Description of the PARDIE cohort stratified by immune status

Variable	PARDS (n = 603)	I-PARDS (n = 105)	p value
Age (years)	2.5 (IQR: 0.6, 8.8)	8.2 (IQR: 2.7, 13.9)	<0.001
Female sex (%)	229 (38.4)	45 (42.9)	0.356
Pre-existing Non-ICC[a] co-morbidities (%)			
Home ventilation	28 (4.6)	0 (0.0)	0.024
Chronic pulmonary disease	180 (29.9)	17 (16.2)	0.004
Prematurity	124 (20.6)	7 (6.7)	0.001
Congenital heart disease	74 (12.3)	4 (3.4)	0.011
Neuromuscular disease	113 (18.7)	9 (8.6)	0.011
Admission source (%) (n = 706)			<0.001[c]
Other intensive care unit	78 (12.9)	13 (12.6)	
Emergency department	305 (50.6)	18 (17.5)	
Inpatient floor/recovery room	208 (34.5)	72 (69.9)	
Other	12 (2.0)	0 (0.0)	
Severity of illness			
PRISM[b] IV (admission) (n = 639)	6 (IQR: 3, 12)	13 (IQR: 5, 18)	<0.001
Geographic region			0.536
North America	385 (63.9)	63 (60.0)	
Europe	102 (16.9)	17 (16.2)	
Central & South America	85 (14.1)	16 (15.2)	
Middle East / Asia / Australia	31 (5.1)	9 (8.6)	

Numbers are presented as medias with interquartile ranges for continuous variables and counts with percentages for the categorical variables.

[a]ICC=immunocompromising conditions,

[b]PRISM= pediatric risk of mortality score,

[c]Overall p value for chi squared analysis. Using pairwise comparison with Bonferroni correction to compare admission sources to each other, those with PARDS had a higher proportion admitted from the emergency department than another ICU (p=0.005) and from an inpatient floor (p<0.001), while those with I-PARDS had a higher proportion admitted from the floor (p<0.001) compared to the emergency department.

Table 2:

Information surrounding pediatric acute respiratory distress (PARDS) diagnosis

	PARDS (n = 603)	I-PARDS (n = 105)	p value
At-risk for PARDS[a] information			
At-risk for PARDS	331 (55.3)	69 (65.7)	0.046
Time at-risk for PARDS from PICU admission (hours)	0 (IQR: −5.0, 3.1)	-1.2 (IQR: −18.0, 5.8)	0.055
Time at-risk for PARDS to PARDS diagnosis (hours)	10.6 (IQR: 3.8, 32.9)	19.9 (IQR: 7.9, 45.6)	0.0024
Location when met at-risk criteria (n=399) Intensive care unit	164 (49.7)	37 (53.6)	< 0.001[c]
Emergency department	90 (27.3)	5 (7.2)	
Ward/Operating room/Recovery room	68 (20.1)	27 (39.1)	
Other	8 (2.4)	0 (0.0)	
PARDS diagnosis information			
PARDS Risk Factor Pneumonia	365 (60.5)	45 (42.9)	< 0.001[d]
Sepsis	97 (16.1)	39 (37.1)	
Aspiration	48 (8.0)	4 (3.8)	
Trauma	27 (4.5)	0 (0.0)	
Pancreatitis	1 (0.2)	2 (1.9)	
Drowning	5 (0.8)	0 (0.0)	
Transfusion related acute lung injury	0 (0.0)	1 (1.0)	
Other	60 (10.0)	14 (13.3)	
Bilateral CXR[a] findings at PARDS diagnosis	437 (72.5)	86 (81.9)	0.042
Location when met PARDS criteria Intensive care unit	546 (90.6)	95 (90.5)	0.272
Emergency department	38 (6.3)	4 (3.8)	
Ward/Operating room/Recovery room	19 (3.2)	6 (5.7)	
Type of ventilation at PARDS diagnosis Noninvasive ventilation	121 (20.1)	40 (38.1)	< 0.001
Invasive mechanical ventilation	482 (79.9)	65 (61.9)	
PALICC categories at diagnosis (%) Non-invasive	121 (20.1)	40 (38.1)	p<0.001[e]
Mild	200 (33.2)	21 (20.0)	
Moderate	144 (23.9)	10 (9.5)	
Severe	138 (22.7)	34 (32.4)	

Data are presented as medias with interquartile ranges for continuous variables and counts with percentages for the categorical variables.

[a]CXR= chest radiograph. Pairwise comparisons with Bonferroni correction were done for multiple comparisons.

[c]Overall p, patients with IPARDS met at-risk criteria in the Emergency department than the intensive care unit (p=0.002) or the ward (p<0.001).

[d] Overall p value, here, those with PARDS had a higher proportion of pneumonia ($p<0.001$) and those with I-PARDS had a higher proportion of sepsis ($p<0.001$),

[e] Overall p-value, Numbers are rounded to the nearest 10^{th} place accounting for some percentages to not equal 100 exactly

Table 3:

Markers of non-pulmonary organ dysfunction and general outcomes

	PARDS (n = 603)	I-PARDS (n = 105)	p value
Markers of non-pulmonary organ dysfunction			
Non-Pulmonary PELOD[a]2 score			
At diagnosis	2 (IQR: 1, 4)	4 (IQR: 2, 6)	<0.001
Day 1	2 (IQR: 1, 4)	5 (IQR: 3, 6)	<0.001
Day 2	2 (IQR: 1, 3)	4 (IQR: 2, 6)	<0.001
Day 3	2 (IQR: 0, 3)	4 (IQR: 2, 6)	<0.001
Neurologic dysfunction			
Neurologic PELOD score >0	31 (5.1)	5 (4.8)	0.870
Cardiovascular dysfunction			
Cardiovascular PELOD score >0	533 (88.4)	86 (81.9)	0.064
Any vasoactive use	218 (36.2)	53 (50.5)	0.005
Vasopressor-inotrope score at diagnosis (n = 621)	0 (0, 10)	4 (0, 20)	0.001
Renal Dysfunction			
Renal PELOD score >0	302 (50.1)	68 (64.8)	0.005
Renal replacement therapy	21 (3.5)	13 (12.4)	<0.001
Fluid balance on day of diagnosis mL/Kg	28.4 (IQR: 5.7, 57.5)	29.1 IQR: (7.1, 61.4)	0.576
Diuretic use	320 (53.1)	71 (67.6)	0.006
Hematologic dysfunction			
Hematologic PELOD score >0	165 (26.4)	80 (76.2)	<0.001
Packed red blood cell transfusion on day of diagnosis	59 (11.1)	28 (30.8)	<0.001
Platelet transfusion on day of diagnosis	20 (3.8)	32 (35.2)	<0.001
Gastrointestinal dysfunction			
Total parental nutrition use	76 (12.6)	40 (38.1)	<0.001
Endocrine dysfunction			
Insulin use	27 (4.5)	16 (15.3)	<0.001
Outcomes adjusted for initial oxygenation equivalent and PRISM IV on admission			
	HR[c]/coeff[d] (95% CI[e])		p value
PICU Mortality	aHR:3.0 (95% CI:1.9, 4.7)		<0.001
90-day Mortality - all	aHR:2.9 (95%CI: 1.9, 4,5)		<0.001
90-day Mortality – Initial non-severe PARDS[b]	aHR 3.4 (95%CI: 2.1, 5.5)		<0.001
90-day Mortality – Initial severe PARDS[b]	aHR 3.1 (95%CI: 1.8, 5.5)		<0.001
90-day Mortality – Max non-severe PARDS[b]	aHR 3.5 (95%CI: 1.7, 7.2)		<0.001
90-day Mortality – Max severe PARDS[b]	aHR: 2.9 (95%CI: 1.9, 4.5)		<0.001

	PARDS (n = 603)	I-PARDS (n = 105)	p value
Causes of death (Total, %)			
Refractory hypoxemia	aHR 1.9 (95% CI: 0.7, 4.6)		0.189
Multiorgan failure	aHR 5.8 (95%CI: 3.1, 10.9)		<0.001
Refractory shock	aHR 4.8 (95% CI: 1.8, 13.2)		0.002
Neurologic death	aHR 1.0 (95% CI: 0.3, 2.9)		0.999
Length of ventilation[f]	sHR: 0.47 (95% CI:0.31, 0.71)		<0.001
Length of PICU stay of survivors	β 6.2 (95%CI: −4.0, 16.5)		0.232

Data are presented as medias with interquartile ranges for continuous variables and counts with percentages for the categorical variables.

[a]PELOD = pediatric end organ dysfunction score. Organ dysfunction was evaluated over the first three days of PARDS. Cox proportional hazard regression models were adjusted for initial oxygenation index and PRISM IV score on admission.

[b]PARDS severity analysis only adjusted for initial PRISM IV.

[c]HR=hazard ratio

[d]coeff=coefficient

[e]CI=confidence interval.

[f]length of ventilation was analyzed with a competing risk model using death as a competing risk.