Subphenotypes Assigned to Pediatric Acute Respiratory Failure Patients Show Differing Outcomes

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To the Editor:

Background

Treatment failure of many clinical trials in critically ill patients with acute respiratory distress syndrome (ARDS) is thought to be due, at least in part, to patient heterogeneity. Latent class analysis of adults with ARDS has consistently identified two subphenotypes distinguished by levels of inflammation (1, 2). Recently, we applied the same latent class analysis methodology used in adult patients with ARDS to patients with pediatric ARDS (PARDS) (3). We determined that patients with PARDS share these same two subphenotypes. Parsimonious models using only three class-defining variables that were previously validated in adult patients with ARDS (4) were also able to classify subphenotypes accurately in children with PARDS, although with different "cutpoints." Using our pediatric data, we generated a parsimonious classifier model with three biomarkers, again with excellent discriminatory ability in assigning patients to each of the subphenotypes.

The parsimonious model also has prognostic value in adults with acute respiratory failure (ARF) but without ARDS (5). We hypothesized that the parsimonious model used with adults and the one derived in children with PARDS would also have prognostic value in children with ARF without PARDS. Therefore, we examined the proportion of patients classified into each phenotype in children with ARF using the parsimonious models and evaluated the prognostic implications of these subphenotypes. Some of these results were presented at the 2022 American Thoracic Society International Conference in San Francisco, California.

Methods

We conducted a secondary analysis of the Randomized Evaluation of Sedation Titration for Respiratory Failure, or RESTORE (U01 HL086622), clinical trial (6) and the Genetic Variation and Biomarkers in Children with Acute Lung Injury, or BALI (R01 HL095410), ancillary study. We identified intubated pediatric patients with ARF secondary to acute airways or pulmonary disease who did not meet the Pediatric Acute Lung Injury Consensus Conference criteria for PARDS oxygenation defect (7) and/or did not have bilateral infiltrates on a chest radiograph with an available sample taken within 2 days of intubation. For patients with more than one sample, we used the earliest sample within that time frame.

We assigned subjects to subphenotypes using both the adult subphenotype classifier model (soluble tumor necrosis factor receptor-1, IL-6, and vasopressor use) (4) and the pediatric, biomarker-only, classifier model (soluble tumor necrosis factor receptor-1, IL-6, and IL-8) (3). Subphenotypes were assigned using a probability cutoff of 0.5, or the cutoff determined by the Youden index derived from the PARDS dataset (3).

Summary statistics (mean, median, and proportions) of baseline clinical and biological characteristics of subphenotypes and differences between characteristics and outcomes (duration of mechanical ventilation [durMV] over 28 days, 90-day in-hospital mortality) of the two subphenotypes were evaluated by Wilcoxon rank-sum, chi-square, or Fisher's exact test as appropriate. The primary outcome, durMV, was defined as it was in the RESTORE trial, with death assigned 28 days, making it equivalent to ventilator-free days (6). Multivariable analysis was performed, adjusting for the indicated clinically relevant variables. R (Version 3.2.5) was used for all analyses. The institutional review board approved this study.

Results

This analysis included 122 children without PARDS; 49% (60/122) were male, 54% were non-Hispanic White (66/122), and median age was 3.3 years (interquartile range [IQR] = 0.7–11.1 yr). The median Pediatric Risk of Mortality (PRISM) III score was 7.5 (IQR = 3–13), and median durMV was 5.0 (IQR = 3.3–9.8). Although mortality was only 11% (13/122), almost half (54/122, 44%) required vasopressors. Using either the adult-derived or pediatric-derived classification algorithms, most patients were assigned to the hypoinflammatory subphenotype (adult classifier algorithm: 102/122, 84%; pediatric classifier algorithm: 96/114, 84%). There was almost perfect agreement between the two classifier models, as indicated by a Cohen's kappa coefficient of 0.87 (95% confidence interval, 0.75–0.99).

Using the adult classifier algorithm, most children with a primary diagnosis of sepsis (12/20, 60%) were assigned to the hyperinflammatory subphenotype (Table 1). Primary diagnoses of children assigned to the hypoinflammatory subphenotype were relatively equally distributed (21–26%), except for those with sepsis (8%, 8/102). Compared with patients assigned to the hypoinflammatory subphenotype, patients in the hyperinflammatory subphenotype exhibited greater severity of illness (PRISM III score: 11.5 [6.0–18.5] vs. 6.5 [3.0–12.0], $P = 0.037$) and higher mortality (9/20 [45%] vs. 4/102 [4%], $P < 0.0001$). Multivariable regression models adjusting

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Table 1. Characteristics of Subphenotypes Assigned Using the Adult and Pediatric Classifier Models

Characteristic	Adult Model (IL-6, TNFR1, and Vasopressor Use)			Pediatric Model (IL-6, IL-8, and TNFR1)		
	Hypoinflammatory (*n* = 102)	Hyperinflammatory (*n* = 20)	*P* Value	Hypoinflammatory (*n* = 96)	Hyperinflammatory (*n* = 18)	*P* Value
Male, *n* (%)	49 (48)	11 (55)	0.63	49 (51)	9 (50)	0.99
Age, yr, median (IQR)	2.6 (0.6–10.2)	10.3 (2.0–14.7)	0.069	3.1 (0.8–10.3)	10.3 (0.9–14.5)	0.20
Non-Hispanic White, *n* (%)	53 (52)	13 (65)	0.33	51 (53)	12 (67)	0.32
Hispanic White, *n* (%)	14 (14)	3 (15)	0.99	13 (14)	2 (11)	0.99
Non-Hispanic Black, *n* (%)	25 (25)	1 (5)	0.071	23 (24)	1 (6)	0.11
Primary diagnosis, *n* (%)						
Pneumonia	27 (26)	7 (35)	<0.0001	28 (29)	5 (28)	0.0004
Asthma	24 (24)	0 (0)		21 (22)	0 (0)	
Bronchiolitis	21 (21)	1 (5)		19 (20)	1 (6)	
Sepsis	8 (8)	12 (60)		8 (8)	11 (61)	
Others	22 (22)	0 (0)		20 (21)	1 (6)	
Medical history, *n* (%)						
Asthma	31 (30)	1 (5)	0.023	28 (29)	1 (6)	0.039
Prematurity	10 (10)	2 (10)	1.0	10 (10)	2 (11)	1.0
Seizure disorder	9 (9)	2 (10)	1.0	9 (9)	1 (6)	1.0
Immunodeficiency*	4 (4)	6 (30)	0.001	5 (5)	5 (28)	0.009
Vasopressor use, *n* (%)	35 (34)	19 (95)	<0.0001	37 (39)	16 (89)	<0.0001
durMV, d, median (IQR)	4.7 (3.0–6.8)	13.5 (8.7–28.0)	<0.0001	4.8 (3.0–7.2)	11.6 (7.8–28.0)	0.0001
PRISM III, median (IQR)	6.5 (3.0–12.0)	11.5 (6.0–18.5)	0.037	6.0 (3.0–12.0)	12.5 (7.2–19.5)	0.002
Died, *n* (%)	4 (4)	9 (45)	<0.0001	4 (4)	9 (50)	<0.0001
IL-6, pg/ml, median (IQR)	11.2 (3.4–39.7)	630.4 (101.9–2,244.6)	na	11.2 (3.3–40.0)	884 (96.6–2,591.5)	na
IL-8, pg/ml, median (IQR)	24.2 (15.2–41.1)	587.3 (124.3–1,673.2)	na	24.7 (15.6–42.0)	693.2 (320.0–1,752.1)	na
sTNFR1, pg/ml, median (IQR)	615.6 (366.5–1,056.7)	3,197.8 (1,920.1–6,103.2)	na	615.6 (361.1–1,088.4)	4,119.9 (2,332.3–7,194.1)	na

Definition of abbreviations: durMV = duration of mechanical ventilation; IQR = interquartile range; na = not applicable, as subphenotypes were determined on the basis of biomarker levels; PRISM III = Pediatric Risk of Mortality III; sTNFR1 = soluble tumor necrosis factor receptor 1; TNFR1 = tumor necrosis factor receptor 1.
*Current and/or past medical history of cancer or other immunodeficiency.

for severity of illness, age, and sepsis diagnosis confirmed that the hyperinflammatory subphenotype was independently associated with both higher mortality (Table 2) and prolonged durMV (coefficient = 9.87 [5.80–13.93], $P < 0.001$).

When applying the pediatric classifier algorithm, 114 patients were included, as not all patients had plasma IL-8 measurements. Unsurprisingly, given the concordance between the adult and pediatric models, the distribution of primary diagnoses across the two subphenotypes, severity of illness at pediatric ICU admission, and mortality were similar to the adult classifier model results. Again, multivariable models adjusting for age, sepsis diagnosis, and PRISM III score indicated a greater risk of death in patients assigned to the hyperinflammatory subphenotype (Table 2), and prolonged mechanical ventilation (coefficient = 7.82 [3.19–12.45], $P = 0.001$).

Discussion

In this group of children with ARF, the pediatric and adult parsimonious models assigned a small (~16%) but significant group to the hyperinflammatory subphenotype, compared with the 40% in the hyperinflammatory subphenotype in patients meeting PARDS criteria from the same study (3). Patients with ARF in the hyperinflammatory group have an increased risk for worse clinical outcomes compared with those in the hypoinflammatory group,

Table 2. Multivariable Regression Analyses for Mortality and Duration of Mechanical Ventilation

Outcome and Variable	Adult Model			Pediatric Model		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Mortality						
Hyperinflammatory subphenotype	13.56	2.43, 92.18	0.004	14.69	2.28, 94.6	0.005
Age, yr	1.11	0.98, 1.26	0.11	1.13	1.00, 1.29	0.057
Sepsis diagnosis	1.48	0.22, 8.78	0.67	1.23	0.18, 8.41	0.83
PRISM III	1.15	1.04, 1.28	0.007	1.13	1.02, 1.26	0.017
Outcome and Variable	**Coefficient**	**95% CI**	***P* Value**	**Coefficient**	**95% CI**	***P* Value**
durMV						
Hyperinflammatory subphenotype	9.87	5.80, 13.93	<0.001	7.82	3.19, 12.45	0.001
Age, yr	−0.003	−0.231, 0.225	0.98	0.07	−0.18, 0.32	0.57
Sepsis diagnosis	−1.03	−5.07, 3.01	0.62	−0.31	−4.75, 4.13	0.89
PRISM III	0.08	−0.12, 0.28	0.42	0.06	−0.17, 0.28	0.61

Definition of abbreviations: CI = confidence interval; durMV = duration of mechanical ventilation; PRISM III = Pediatric Risk of Mortality III.

indicating that subphenotype assignment also has strong prognostic relevance in children with ARF but not PARDS.

Recent investigations in adults with ARF without ARDS also support the existence of two subphenotypes with characteristics similar to those seen in patients with ARDS, again distinguishable by inflammatory biomarkers and by clinical outcomes (5, 8). Thus, these two subphenotypes share overlap across the adult and pediatric ARF spectra, offering a rationale for innovative trial enrollment strategies across ages.

Our findings emphasize the challenge of syndromic definitions such as PARDS in specific, and ARF in general, which struggle to identify and characterize complex pathophysiologic processes that culminate from multiple inciting diagnoses. Our data suggest that the complex inflammatory pathways and inflammatory-related subphenotypes associated with PARDS (3, 9) are also involved in children with ARF, and recent data suggest that they may also be observed in other critically ill children (10).

In conclusion, these data suggest that parsimonious model subphenotype assignment can enable robust prognostic enrichment compared with prior risk stratification schema. Earlier identification of high-risk subphenotypes, particularly in pediatric patients, could result in earlier escalation of care in patients at greater risk for complex course.

After validation, these data may impact future clinical trial design, including the expansion of subphenotype identification to the broader pediatric ARF cohort. ■

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Right Ventricular Response to Acute Hypoxia among Healthy Humans

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