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Identification of phenotypes in paediatric patients with acute respiratory distress syndrome: a latent class analysis

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Contributor Statement

MKD and HF equally conceptualized, curated data, formalized the analysis, acquired funding, determined methodology, supervised and administered all aspects of the investigation, curated and analyzed the data, validated the data and completed the original draft. HW curated data and formalized the analysis. MZ formalized the analysis and methodology, provided statistical support, supervised the statistical analysis, validated the data and participated in writing the manuscript. GY curated the data, completed the formal analysis including data visualization, validated data, and participated in writing of the manuscript. MQ and AS were each key investigators for the original patient acquisition, and acquisition of resources for this study, reviewed the analysis and participated in interpretation of results. MC was the primary investigator of the parent randomized controlled study that provided the needed patient data, contributed to the design of the study, assisted in funding acquisition, and reviewed the analysis. KD and CC equally assisted in the conceptualization of this research, assisted in funding acquisition, and formalized the methodology. PS contributed to the methodology and analysis and assisted in the statistical analysis. All authors contributed to interpretation of data, and all authors reviewed, and approved, the final manuscript. MKD, and HF, have accessed and verified the data and are responsible for the decision to submit the manuscript.

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Data Sharing

Deidentified individual participant data and the data dictionary for this study will be shared through the BIOLINCC repository managed by the NHLBI. Data will be shared within one year of publication of the results.

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Abstract

Background: Latent class analysis (LCA) identified two phenotypes, distinguished by the degree of inflammation, in adults with acute respiratory distress syndrome (ARDS). No studies have used LCA to identify phenotypes in children with ARDS where developmental differences may be important.

Methods: This secondary analysis used 304 children with pediatric ARDS (PARDS) enrolled in the *RESTORE* and *BALI* studies. Using methodology developed in adults, this LCA included demographic, clinical, and plasma biomarker variables to identify PARDS phenotypes. The association of phenotypes with clinically relevant outcomes and the performance of pediatric data in adult ARDS classification algorithms was examined.

Findings: Using LCA, a two-class model was a better fit for the group than a one-class model ($p<0.001$); additional classes did not improve fit. One class was characterized by higher levels of inflammatory biomarkers, greater vasopressor use, and more frequent diagnosis of sepsis, consistent with the adult "hyper-inflammatory" phenotype. PARDS severity levels spanned both phenotypes. Children with the hyperinflammatory phenotype experienced a longer duration of mechanical ventilation (10.0d vs 6.6d, $p<0.0001$), and higher mortality (13.8% vs 2.2%, $p=0.0001$). In children, adult phenotype classification algorithms using sTNFr1, vasopressor use and either IL-6, or IL-8, had AUCs of 0.956 and 0.954, respectively, compared to the gold standard of LCA class.

Interpretation: LCA identified two phenotypes in PARDS with characteristics similar to those in adults, including worse outcomes in the hyperinflammatory phenotype. PARDS phenotypes should be considered in design and analysis of future clinical trials in children.

Keywords

biomarkers; endotype; children; ARDS

Introduction

Even prior to the SARS-CoV2 pandemic, acute respiratory distress syndrome (ARDS) was a global problem with the study of Bellani and colleagues across 50 countries showing ARDS accounting for 10.4% of intensive care unit (ICU) admissions, with an alarmingly high mortality rate of 40%.[1] ARDS results from a variety of disease states, affects critically ill adults and children, and is associated with extremely high morbidity and mortality across all age groups.[1–3] Pharmacologic treatment has to date proven ineffective in decreasing ARDS mortality,[4] and clinical and biological heterogeneity likely contributes to the failure of the treatments tested thus far.[5] Studies using latent class analysis (LCA) of data derived from multiple large, adult ARDS trials have identified two phenotypes with differing clinical outcomes in adult ARDS patients.[6–9] Clinical factors and plasma biomarkers, acting as indicators of underlying pathophysiology, can distinguish these phenotypes with one termed "hyperinflammatory" and the other "hypoinflammatory." The two phenotypes appear to

be stable for at least three days after meeting ARDS criteria.[10] In some cases, secondary analysis indicated that each phenotype responded differently to treatment, even though no treatment effects were observed in the original clinical trial.[6–8] Recently, Sinha et al have developed and validated parsimonious algorithms using biomarkers and clinical data to classify ARDS patients into the phenotypes identified by LCA.[11] Although only two different ARDS phenotypes have been described using LCA thus far, other phenotypes may exist, particularly in children where additional developmental and age-related factors are present. To date, no studies have used LCA to identify pediatric ARDS (PARDS) phenotypes.

The main objective of this research was to identify phenotypes in children with PARDS using an LCA approach similar to that done in adult ARDS patients. Our hypothesis was that there are multiple phenotypes in children with PARDS which differ in their underlying pathophysiology. If the heterogeneous group of children with PARDS can be separated into distinct phenotypes, and these phenotypes differ in their pathophysiology, then they may also differ in responsiveness to therapies, as is suggested by the data in adults with ARDS.[6–8] Consequently, future therapeutic trials in PARDS could use phenotype assignment to stratify PARDS patients in treatment trials and/or develop treatment strategies more precisely targeted to specific PARDS phenotypes.

Methods

Study Design

This is a secondary analysis of children with PARDS in the *Randomized Evaluation of Sedation Titration for Respiratory Failure* multi-site clinical trial (*RESTORE*; U01 HL086622) and its ancillary study, *Genetic Variation and Biomarkers in Children with Acute Lung Injury* study (*BALI*; R01HL095410), which together prospectively enrolled and obtained plasma samples from children with acute respiratory failure. The study was approved the Institutional Review Board at the University of Michigan. Details of the inclusion and exclusion criteria have been published previously[12] and are outlined in the supplement which also includes details related to the cohort used for this analysis. PARDS was defined using the Pediatric Acute Lung Injury Consensus Conference[13] criteria for oxygenation index (OI) or oxygen saturation index (OSI) with the presence of acute-onset, bilateral infiltrates on chest radiograph, as described previously.[12]

Biomarker Measurements

Biomarker measurements are described in the supplement.

Statistical Analysis

LCA was used to identify subgroups within the cohort of children with PARDS as described by Sinha et al.[14] LCA is a form of finite mixture modeling wherein a series of models are fit to data under the assumption that the observed multivariate distribution is the result of a mixture of distributions. LCA has the advantage that it defines subgroups by considering multiple variables concurrently without considering outcome. The children enrolled in *BALI* are a subset of the children enrolled in *RESTORE*;[15] consequently a rich dataset of clinical

and demographic variables was available that had onsite auditing and data quality checks with a low degree of missingness. Primary diagnosis, defined as the primary reason for the acute respiratory failure resulting in intubation, was taken from the medical record.[12, 15] The demographic, clinical and biomarkers variables included as potential class defining variables in the LCA (Tables S1 and S2) were guided by the studies in adults.[6, 7, 10] Some variables were modified to be more appropriate for a PARDS cohort. Details related to the variables and the LCA are described in the supplement.

To evaluate the distinguishing features of the identified classes, summary statistics (mean, median, proportions) of baseline clinical and biological characteristics of each class were examined after assigning study participants to their most likely class using LCA. Differences in outcomes (duration of mechanical ventilation, 90 day in-hospital mortality) across classes was tested by Wilcoxon rank-sum or Fisher's test as appropriate. Duration of mechanical ventilation was the primary outcome defined as it was in the *RESTORE* trial as the time of intubation (or PICU admission in those transferred intubated from another hospital) to the first time the endotracheal tube was removed for at least 24 hours examined over 28 days.[15] Those who died prior to day 28 were assigned the highest number of days of mechanical ventilation (28 days) making this outcome equivalent to the ventilator-free day outcome measure used in all prior adult ARDS LCA analyses.[16] To examine whether the classes responded differently to the targeted sedation protocol of the *RESTORE* trial, models of each outcome (duration of mechanical ventilation, mortality) were examined using class, treatment assignment, and their interaction as covariates.

Two approaches were used to examine whether the classes identified by LCA could be defined by a limited set of biomarkers. In the first approach classifier models were created using the pediatric dataset where the assigned classes were treated as dependent variables. The two or three biomarkers that exhibited the greatest difference in mean absolute values between classes identified by LCA in the pediatric data (sTNFr1, IL-6, IL-8) were chosen, and as described in the first adult LCA studies, the Z scores of these biomarkers were used in the models.[6, 7] Logistic regression was used to identify model coefficients and classes were assigned using a probability cutoff of ≥0.5 or the cutoff determined by the Youden index. Calibration plots were created to evaluate model calibration. In the second approach, we examined whether the adult algorithms also defined phenotypes in children using three-variable algorithms identified and validated in adults:[11] combinations of two biomarkers (sTNFr1, and IL-6 or IL-8) and vasopressor use. We chose to test the algorithms using these variables from the several options developed for use in adults[11] because our dataset did not include data on levels of bicarbonate. As described for the adult ARDS algorithms, a value of 1 was added to the measured biomarker value prior to log transformation and use in the model.[11] Classes were assigned using a probability cutoff of ≥0.5 or the cutoff determined by the Youden index derived in the pediatric dataset using the adult algorithms. The area under the curve (AUC), sensitivity and specificity, and the Bayesian Information Criterion (BIC) are reported for all models.

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Results

The general characteristics of the group of 304 children with PARDS (Table S3) are very similar to those for the total group of children with PARDS reported previously with slightly more than half being male, pneumonia being the most common reason for intubation, followed by acute respiratory failure related to sepsis and bronchiolitis.[12] History of asthma and prematurity were the most common comorbidities. Approximately half of the cohort was treated with vasopressors.

To explore whether children with PARDS could be separated into different classes, LCA was done using the demographic, clinical and biomarker variables listed in Tables S1 and S2. Although LCA can handle missingness, there was relatively low missingness in the data with 21 of the 35 variables having ≤5% missing and only six having between 20% and 31% missing. Results of the LCA demonstrated that a two-class model best fits the data, as indicated by the fit statistics shown in Table 1. The VLMR test indicated that the two-class model fit the data better than one-class with an entropy of 0.908, indicating good separation between the classes. The average latent class probabilities for Class 1 and 2 were 0.973±0.082, and 0.973±0.081, respectively. Class 1 and Class 2 comprised 60% (n=181) and 40% (n=123) of the PARDS patients, respectively. For simplicity, the two classes will be referred to as phenotype 1 and 2, respectively.

Characterization of the two phenotypes was done by assigning children to their most likely phenotype and then examining the demographic, clinical, and biomarker profiles of each phenotype. Shown in Figure 1 are the scaled continuous variables used in the analysis sorted by the degree of separation between phenotypes. The variables with the greatest degree of separation are primarily plasma biomarkers. Phenotype 2 is characterized by markedly higher levels of inflammatory cytokines (Table 2), in a similar pattern to that observed in the hyperinflammatory phenotype in adults. The proportion of children with mild, moderate, and severe PARDS varied between phenotype 1 and 2 (p=0.0001). In phenotype 1, 32% of children had mild PARDS, 39% had moderate PARDS and 29% had severe PARDS. Approximately half (53%) of children in phenotype 2 met severe PARDS criteria, while 47% of phenotype 2 consisted of children with mild or moderate PARDS (Figure 2). The proportion of males and Hispanic Whites were similar across phenotypes (Figure S1) while phenotype 2 had slightly more Non-Hispanic Whites (66% versus 47%, p=0.001) and fewer Non-Hispanic Blacks (5% versus 24%, p<0.0001). PARDS triggered by virally induced bronchiolitis, was a more common PARDS risk factor in phenotype 1 than phenotype 2 (28% versus 6%, respectively, p<0.0001), while PARDS triggered by sepsis was a more common risk factor in phenotype 2 than 1 (39% versus 7%, respectively, p<0.0001). Phenotype 2 also had a higher proportion of children with vasopressor use (80%

versus 35%, p<0.0001) and a higher median age than phenotype 1 (Table S4). Values of continuous variables for each phenotype are shown in Tables S4 and S5.

Clinical outcome differed by phenotype (Table 3). The children with PARDS in phenotype 2 exhibited worse outcomes than those in phenotype 1 with a longer duration of mechanical ventilation (10.0 versus 6.6 days, p<0.0001) and higher mortality (13.8% vs 2.2%, p=0.0001). The median length of mechanical ventilation in survivors was also significantly longer in children in phenotype 2 compared to 1 (8.7 [IQR 5.5–15.4] versus 6.4 [4.1–10.5], respectively, p=0.003). We also examined whether there were differences in outcomes between phenotypes in response to the targeted sedation protocol which was the intervention in the *RESTORE* trial. We observed no significant interaction between phenotype and the targeted sedation strategy on either the duration of mechanical ventilation or the frequency of mortality (Table S6).

To examine whether the two phenotypes could also be robustly identified by two or three variables, we examined how well the variables with the greatest mean difference in values predicted the assigned phenotype using receiver operator characteristic curve analysis. The variables used were IL-6, IL-8, and sTNFr1. The predictor model with all three variables yielded an AUC of 0.977 (Table S7). The model including just IL-6 and sTNFr1 performed just as well as the three-variable model, with a similar AUC (0.976), however these findings will need to be validated in an external cohort. The AUCs and Youden index were also calculated based on a leaving-one-out cross validation approach and showed almost identical numbers. Calibration plots also showed good model calibration (Figure S2). To determine how well classifier algorithms developed and validated in adults identified phenotypes in children, we examined the performance of the adult three-variable algorithms which included sTNFr1, vasopressor use and either IL-6, or IL-8; the gold standard was phenotype as assigned by the LCA. As shown in Table 4, when using model coefficients identified in adults with ARDS, the parsimonious, three-variable adult model showed a high AUC but had poor sensitivity when probability ≥0.5 was used to assign phenotype. However, if the cutoff chosen by the Youden index in this pediatric PARDS cohort was used to assign phenotype, the sensitivity increased substantially.

Discussion

Through LCA, we found evidence that the group of children with PARDS encompasses two phenotypes, each with distinct clinical and biological characteristics and divergent clinical outcomes. PARDS phenotype 2 is characterized by higher levels of inflammatory biomarkers, a higher proportion of patients with sepsis and more patients with a need for vasopressors. PARDS phenotype 1 has lower levels of inflammatory cytokines (though still elevated) and a higher proportion of patients admitted with bronchiolitis as a PARDS risk factor. In comparison to phenotype 1 patients, children in phenotype 2 experience worse clinical outcomes including a longer duration of mechanical ventilation and greater mortality. These two phenotypes share striking resemblance to the phenotypes described previously in multiple adult ARDS latent class analyses.

Unlike the LCA done in adults, several vital sign components and laboratory values included in the LCA required age dependent evaluation of data because of the maturational changes which occur from birth to young adulthood in the pediatric population. Such changes include maturation of the immune system, the lung parenchyma, and the chest wall. Remarkably, despite these maturational differences, there are many similarities between the results reported here in children and those reported in adults including fit statistics strongly supporting two phenotypes, worse clinical outcomes in phenotype 2 compared to phenotype 1, and the identification of the same biomarkers (sTNFr1, IL-6 and IL-8) as the variables with the largest difference between phenotypes. Application of two adult classifier algorithms[11] to our PARDS cohort yielded AUCs of 0.956 (sTNFr1, vasopressor, IL-6) and 0.954 (sTNFr1, vasopressor, IL-8), respectively. Although the algorithms had high AUCs they had poor sensitivity when not using the cutpoint identified by the Youden index determined in the pediatric cohort for class assignment. Together these observations suggest that while there are many similarities between the PARDS and ARDS phenotypes, differences remain including a likely need for different cutpoints in children that must be tested in future phenotype classification models. It is also possible that there are other underlying differences between the pediatric cohort examined here and the adult cohorts unrelated to age.

This PARDS LCA revealed the distribution of mild, moderate, and severe PARDS patients across both phenotypes. Although PARDS severity is associated with clinical outcomes,[17] this LCA supports inherent pathophysiologic differences between individuals in response to critical illness that transcends severity level and may need to be accounted for to optimize treatment. The breadth of PARDS severities across phenotypes may also be, at least in part, related to the patient cohort examined (acute respiratory failure due to primary pulmonary or airways disease), thus warranting validation in other PARDS cohorts in the future. In addition, while the PARDS cohort used for this LCA had a similar proportion of individuals with pneumonia and sepsis as seen with adults, the group also included many patients with a primary viral trigger and subsequent PARDS development. Of patients with an initial viral bronchiolitis diagnosis and subsequent PARDS development, most (88%) are included in phenotype 1, while the majority of the patients with a primary diagnosis of acute respiratory failure due to sepsis (79%) are assigned to phenotype 2. However, we do not believe that the main differences between the two phenotypes are based on aetiology. Patients with bronchiolitis make up only 28% of all the PARDS patients in phenotype 1; 38% of patients in phenotype 1 have a diagnosis of pneumonia and 27% have one of the less common diagnoses. In phenotype 2, patients with sepsis make up only 39% of the group; 40% have a diagnosis of pneumonia and 16% have one of the less common diagnoses. LCA appears to provide a more robust way to identify patients with common underlying characteristics and the variables that best distinguish the phenotypes identified are the biomarkers, not the primary diagnoses.

Although respiratory syncytial virus (RSV) is the most common cause of bronchiolitis, this study could not dissect out the individual viral triggers, or possible bacterial coinfection. While bronchiolitis is often due to infection with RSV, other, potentially more virulent, viruses account for a significant number of bronchiolitis associated PICU admissions. Bronchiolitis is also often associated with viral or bacterial coinfection. In addition, it is

well known that the response to different viral pathogens, and the severity of that response (including the development of ARDS), varies substantially between individuals and across age groups. Clearly the impact of viral disease on ARDS phenotype classification will continue to be a subject in future studies.

To our knowledge, this report is the first use of LCA to identify PARDS phenotypes in children, although previous studies also support the likelihood that subgroups exist. Recently, a study of children with acute hypoxemic respiratory failure secondary to sepsis showed that pediatric septic shock endotypes are also present in children with acute hypoxemic respiratory failure.[18] In addition, plasma biomarkers have been successfully used to derive a PARDS Biomarker Risk Model (PARDSEVERE), though this model is not yet validated.[19] IL-8, one of the variables with the largest difference in level between the phenotypes identified by our LCA, is also one of three biomarkers that remained in the final PARDSEVERE model. It is unclear how the PARDS LCA phenotypes described here relate to the groups identified in the PARDSEVERE model, but it is likely that there is overlap. Future studies examining molecular phenotyping should clarify the relationships between phenotypes/endotypes identified by different methodologies. In adults, recent studies have demonstrated that LCA-derived phenotypes and cluster-derived phenotypes in mechanically ventilated adults with or without ARDS had similar gene expression profiles, implying that prognostic and potentially predictive enrichment may extend beyond PARDS, to patients with acute respiratory failure in general.[20]

In adult studies of ARDS patients, differential treatment response between the hyperinflammatory and hypoinflammatory phenotypes have been reported for three of the four clinical trials where examined. Treatments that appear to be affected by phenotypes include positive end expiratory pressure strategy,[7] fluid management,[6] and simvastatin treatment;[8] there was no differential effect of rosuvastatin treatment.[9] The *RESTORE* clinical trial showed no effect of the targeted sedation protocol on the duration of mechanical ventilation. However, those randomized to the sedation protocol experienced fewer days of opioid administration and were exposed to fewer sedative classes.[15] As recent pediatric studies indicate that sedative clearance is decreased in the face of inflammation,[21, 22] we examined whether there were differences in outcomes between phenotypes in response to the targeted sedation protocol. PARDS phenotype did not affect the impact of the use of the sedation protocol studied in the *RESTORE* trial. This finding is not surprising since our group of PARDS patients was relatively small, and some treatments will be ineffective or effective regardless of phenotype.

Our study had limitations. Sample size for this analysis is relatively modest and does not include a validation cohort. Fortunately, our sample size was large enough to use LCA (n=304 children), and our fit statistics robustly identified two phenotypes. However, future LCA in PARDS patients should include more patients if possible, particularly when examining the impact of phenotype on trial intervention. Infants < 30 days of age are also not that well represented in this analysis and thus few if any conclusions can be made related to this age group. Expansion of this work and validation across PARDS diagnosis associated with patients largely excluded from the *RESTORE* trial, such as the surgery cohort, are also warranted. Finally, another limitation in our analysis comparing our LCA to those completed

in adult ARDS patients is that we did not have perfect overlap of the clinical data collected (e.g. bicarbonate). Nonetheless, our group of clinical variables did match substantively.

In summary, this study demonstrates that the two PARDS phenotypes identified by LCA are very similar to the two LCA phenotypes identified in adults. In both adult and pediatric ARDS LCA, the phenotype exhibiting hyperinflammation, cardiovascular compromise, and a greater proportion of sepsis patients, experience worse clinical outcomes. The finding that these two phenotypes are distinguished by the degree of inflammation may eventually allow phenotype targeted pharmacologic treatments and a personalized medicine approach for PARDS patients. Such a possibility is also suggested by the difference in response to treatments seen in some of the LCA studies of adult ARDS patients.[6–8] Our data do suggest that while adult three-variable classification algorithms do surprisingly well in the pediatric cohort, the sensitivity is quite low without use of the Youden index, suggesting these models will need to be refined using additional PARDS cohorts. It is imperative that novel diagnostics be developed to allow these biomarkers to be measured in real time; a prospective clinical trial of such a device is currently ongoing in the UK (NCT04009330).[23] Finally, it will be important for future clinical trials to consider PARDS phenotypes in study design and analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

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Research in context

Evidence before this study

Data derived from multiple large, adult acute respiratory distress syndrome (ARDS) randomized controlled trials (RCTs) have identified two phenotypes with differing clinical and biological characteristics, termed hyperinflammatory and hypoinflammatory phenotypes. These phenotypes differ in patient outcomes, and, in many studies, in response to RCT treatment group assignment. Recently, parsimonious algorithms have been developed and validated that use a subgroup of the original latent class analysis (LCA) biomarker and clinical variables to classify adult ARDS patients into the two phenotypes identified by the original LCA. We searched PubMED for any study reporting use of LCA to identify phenotypes in pediatric ARDS (PARDS) from database inception to May 6, 2021, using the terms ("ARDS" or "PARDS" or "acute lung injury") AND ("subtype" OR "subphenotype" OR "endotype") AND ("pediatric" OR "children") without language restrictions and found no reports that LCA has been used to identify phenotypes in children with pediatric ARDS (PARDS), where additional developmental and age-related factors may impact the number, or characteristics, of phenotypes.

Added value of this study

This study reports the identification of two phenotypes in children with PARDS using LCA, a hypoinflammatory (phenotype 1) and hyperinflammatory phenotype (phenotype 2). These two phenotypes are similar to those reported in the LCA of adults with ARDS, with phenotype 2 characterized by higher levels of many of the same inflammatory biomarkers elevated in the hyperinflammatory phenotype seen in adults and worse clinical outcomes, including longer duration of mechanical ventilation, and higher mortality, compared to phenotype 1. This study also indicates that there are characteristics unique to the pediatric phenotypes, including a broad distribution of mild, moderate, and severe PARDS patients across both phenotypes and a high proportion of children with bronchiolitis as a PARDS risk factor in phenotype 1, also evidenced by the younger median age in this phenotype. Our pediatric data showed that the three-variable phenotype classification algorithms developed in adults had good discriminatory power (AUCs ~0.95) in children but the optimal cutpoint for phenotype discrimination appears to differ between adults and children. Together these data suggest that although children and adults with ARDS share two strikingly similar phenotypes, nuanced differences between phenotypes in children and adults may exist.

Implication of all the available evidence

Failure of many clinical trials in ARDS patients is thought to be due, at least in part, to patient heterogeneity. In adults, LCA has identified two phenotypes distinguished by underlying differences in the degree of inflammation. The study described here indicates that very similar phenotypes can be identified in children with PARDS. The finding that these two phenotypes are distinguished by the degree of inflammation may eventually allow phenotype targeted pharmacologic treatments and a personalized

medicine approach for PARDS patients. Consideration of these phenotypes will be important in the design and analysis of future clinical trials focused on PARDS.

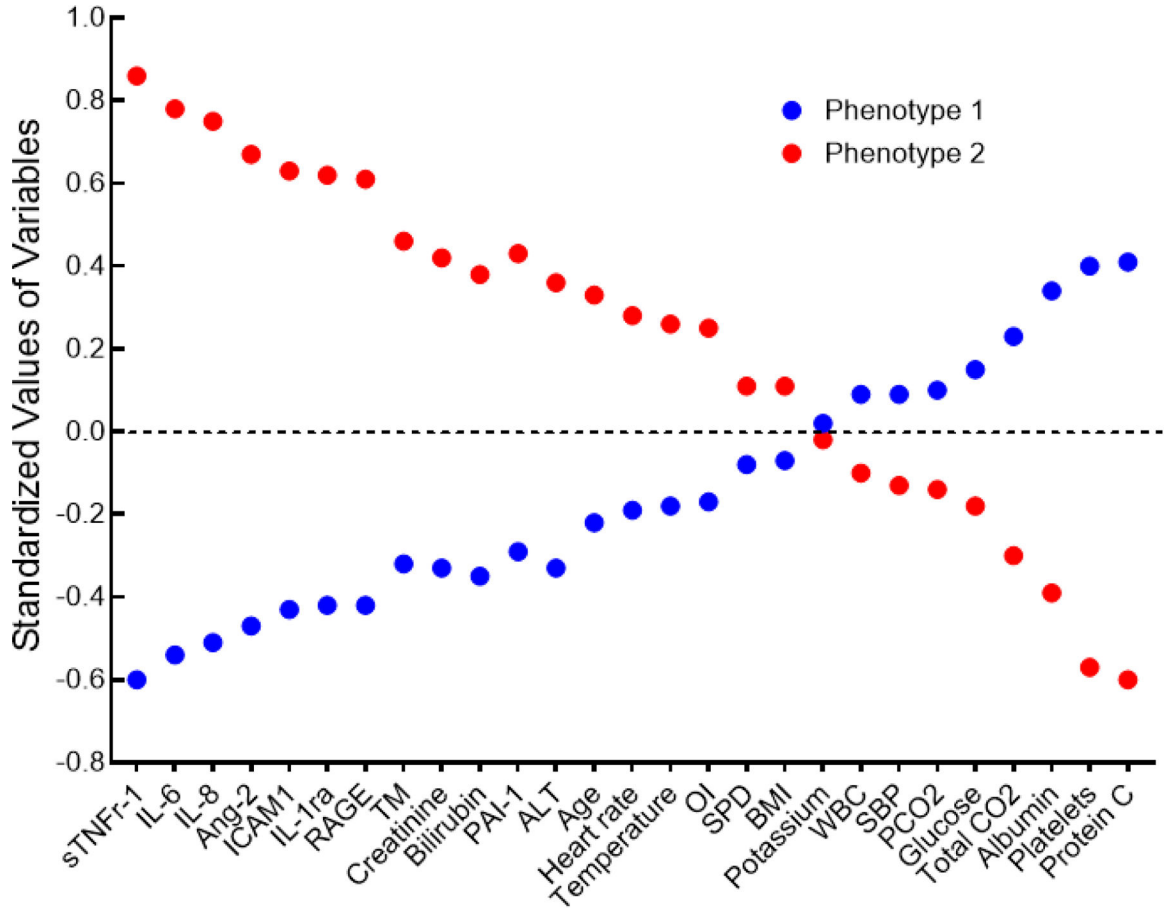

Figure 1. Differences between phenotypes in the standardized values of continuous variables.

Individual continuous variables were put on a z scale with a mean of zero and standard deviation of 1. Standardized variable values for each phenotype represent their variation from the mean in the overall cohort. Variables are listed left to right according to the amount of separation between phentoypes 1 and 2; on the left side of the graph standardized values are higher in phenotype 2, on the right side of the graph standardized values are lower in phenotype 2. Ang-2, angiopoietin-2; ICAM1, intercellular adhesion molecule 1; IL-1ra, interleukin-1 receptor antagonist; IL-6, interleukin-6; IL-8, interleukin-8; PAI-1, plasminogen activation inhibitor 1; RAGE, receptor for advanced glycation end products; sTNFr1, soluble tumor necrosis factor receptor-1; SPD, surfactant protein D; TM, thrombomodulin.

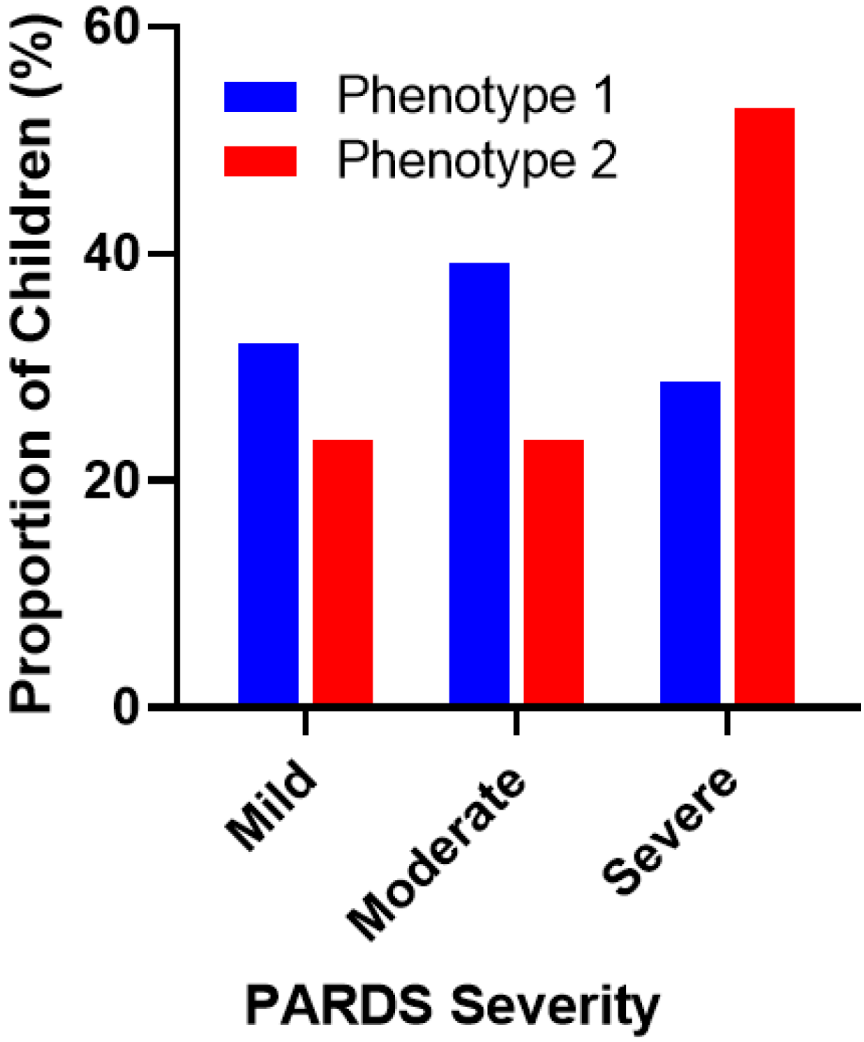

Figure 2. Pediatric acute respiratory distress syndrome severity level by phenotype.

Shown is the proportion of children in each phenotype with the indicated pediatric acute respiratory distress syndrome (PARDS) severity level. The proportion of children with mild, moderate and severe PARDS varies between the hypo- and hyperinflammatory phenotype (p=0.0001). phenotype 1, n=181; phenotype 2, n=123.

Table 1.

Fit statistics for latent class models from one to five classes

N classes	BIC	Entropy	N_1	N_2	N_3	N_4	N_5	VLMR p
1	23869.20	--	304					--
2	22952.26	0.908	181	123				<0.001
3	22763.33	0.934	157	123	24			0.18
4	22738.28	0.906	120	93	66	25		0.33
5	22755.08	0.896	81	76	69	53	25	0.73

BIC = Bayesian Information Criterion; VLMR = Vuong-Lo-Mendell-Rubin test

Table 2.

Biomarkers levels stratified by phenotype

Plasma Biomarkers	Phenotype 1		Phenotype 2	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Angiopoietin-2 (pg/ml)	5484 (4755)	4198 (2395–6900)	16204 (15406)	11930 (7373–19576)
Interleukin-1 receptor antagonist (pg/ml)	4361 (6229)	1738 (799–4413)	12066 (9962)	10600 (4370–16200)
Interleukin-6 (pg/ml)	44 (86)	13 (5–43)	1905 (6058)	207 (72–676)
Interleukin-8 (pg/ml)	60 (198)	28 (17–56)	803 (1676)	118 (71–509)
Intercellular adhesion molecule 1 (ng/ml)	382 (213)	341 (243–470)	932 (571)	781 (525–1166)
Plasminogen activator inhibitor-1 (ng/ml)	60 (52)	40 (20–84)	130 (109)	104 (46–179)
Protein C (% normal plasma)	64.9 (22.7)	63 (49–78)	41 (18)	39 (28–53)
Receptor for advanced glycation end products (pg/ml)	4491 (6619)	2668 (1836–4465)	11263 (9921)	8008 (3970–16041)
Surfactant protein D (ng/ml)	16 (17)	11 (7–17)	21 (24)	14 (8–26)
Thrombomodulin (ng/ml)	105 (56)	96 (66–126)	180 (132)	140 (101–208)
Soluble tumor necrosis factor receptor-1 (pg/ml)	1640 (673)	1545 (1199–1974)	6430 (6794)	4140 (3069–6238)

SD, standard deviation; IQR, interquartile range

Table 3.

Clinical outcome differs between phenotypes

Clinical Outcomes	Phenotype 1	Phenotype 2	p *
Duration of MV, days, median (IQR)	6.6 (4.1–10.8)	10.0 (6.3–21.0)	<0.0001
Mortality, n (%)	4 (2%)	17 (14%)	0.0001

* determined by Wilcoxon rank sum test or Fisher exact test, as appropriate; MV, mechanical ventilation; IQR, interquartile range; Phenotype 1, n=181; phenotype 2, n=123

Table 4.

Phenotype classifier models using adult three-variable algorithms

Variable	Model Coefficients					Model Characteristics						
	Intercept	IL-6	TNFr1	IL-8	Vaso use	AUC (95% CI)	Probability ≥0.5		Youden index			BIC
							Sensitivity	Specificity	Sensitivity	Specificity	Cut Point	
TNFr1, IL-6, vasopressor	−19.446	0.9107	1.4711	-	2.0793	0.956 (0.936–0.976)	0.35	1.00	0.89	0.88	0.068	324.6
TNFr1, IL-8, vasopressor	−18.476	-	1.3367	1.3013	2.3439	0.954 (0.931–0.976)	0.69	0.95	0.91	0.89	0.258	161.6

AUC, area under the curve; BIC, Bayesian Information Criterion; CI, confidence interval; IL-6, interleukin-6; IL-8, interleukin-8; sTNFr1, soluble tumor necrosis factor receptor-1; Vaso, vasopressor; n=288 and 252, for model with IL-6 or IL-8, respectively