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ORIGINAL

Subtypes of pediatric acute respiratory distress syndrome have different predictors of mortality

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Abstract

Purpose: Acute respiratory distress syndrome (ARDS) is heterogeneous in etiology, which may affect outcomes. Stratification into biologically-defined subtypes may reduce heterogeneity. However, it is unknown whether pediatric ARDS has clinically relevant subtypes. We aimed to determine whether clinical characteristics and predictors of mortality differed between direct and indirect ARDS, and separately between infectious and non-infectious ARDS.

Methods: This was a single center, prospective cohort study of 544 children with ARDS (Berlin) between July 2011 and June 2017, stratified into direct versus indirect ARDS, and separately into infectious versus non-infectious ARDS. Multiple logistic regression was used to test for predictors of mortality in the entire cohort, and separately within subtypes. Effect modification by subtype was assessed using interaction tests.

Results: Direct ARDS had lower severity of illness ($p < 0.001$) but worse oxygenation ($p < 0.001$), relative to indirect. Predictors of mortality were similar for direct and indirect ARDS. When comparing infectious and non-infectious ARDS, infectious ARDS had lower severity of illness ($p < 0.001$), worse oxygenation ($p = 0.014$), and lower mortality ($p = 0.013$). In multivariable analysis, immunocompromised status demonstrated effect modification between infectious and non-infectious ARDS ($p = 0.005$ for interaction), with no association with mortality in non-infectious ARDS.

Conclusions: In children, direct and indirect ARDS have distinct clinical characteristics, but similar outcomes and similar predictors of mortality. In contrast, infectious and non-infectious ARDS demonstrate heterogeneity of clinical characteristics, mortality, and predictors of mortality, with traditional predictors of ARDS mortality only applicable to infectious ARDS.

Keywords: ARDS, PARDS, Children, Direct ARDS, Infectious ARDS

Introduction

Acute respiratory distress syndrome (ARDS) encompasses multiple diverse etiologies, leading to significant variability in clinical presentation. Patient heterogeneity may contribute to the absence of therapies for ARDS, despite multiple trials, predominantly in adults. Subclassification of ARDS into subtypes is one approach for reducing heterogeneity. In adults, ARDS has been divided into direct (pulmonary) and indirect (non-pulmonary) etiologies [1–3], infectious or non-infectious [4], focal versus non-focal radiographs [5], and on the basis of biomarkers [1, 6]. One shortcoming of phenotyping using biomarkers is their inaccessibility at bedside. Prior studies have shown that direct and indirect ARDS are associated with biomarker profiles consistent with predominantly alveolar epithelial versus endothelial damage, respectively [1]. Therefore, it is possible that

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subtyping based on readily available clinical data could prove similarly informative.

To date, no studies have queried whether relevant subgroups exist in pediatric ARDS. Additionally, while several studies have tested for predictors of mortality in pediatric ARDS [7–9], no study has assessed whether prognostic factors differ between subtypes. The goal of the present study was to determine whether clinical characteristics and predictors of mortality differed between direct and indirect ARDS, and separately between infectious and non-infectious ARDS, in a large, well-phenotyped pediatric cohort.

Take-home message

Subtypes of pediatric ARDS have different predictors of mortality. Immunocompromised status, a traditional predictor of mortality, is only germane to infectious ARDS etiologies.

Methods

Patient selection

This was an analysis of an ongoing prospective cohort, approved by the Children's Hospital of Philadelphia's (CHOP) Institutional Review Board (IRB), with requirement for informed consent waived. The cohort has previously been described in detail [10]. Briefly, intubated children meeting American-European Consensus Conference criteria for acute lung injury (two consecutive $Pao_2/Fio_2 \leq 300$ separated by ≥ 1 h with bilateral infiltrates) admitted to the CHOP pediatric intensive care unit (PICU) between July 1, 2011 and June 30, 2017 were enrolled. As the study was initiated prior to the Berlin definition [11], minimum PEEP was not specified; however, CHOP PICU does not utilize PEEP < 5 cmH_2O. Thus, all patients met Berlin criteria. Similarly, as the study was initiated prior to the Pediatric Acute Lung Injury Consensus Conference (PALICC) definition of pediatric ARDS (PARDS) [12], we did not screen using OI; however, all but one patient met PARDS criteria by OI.

Demographics, ventilator settings, Pao_2/Fio_2 and OI at ARDS onset and 24 h, and treatments for the first 3 days were recorded prospectively. Absent a standardized ventilator protocol, our practice is to initiate conventional ventilation with PEEP ≥ 5 cmH_2O, and to wean Fio_2 to ≤ 0.60, keeping $PaO_2 \geq 60$ mmHg. Inability to wean Fio_2 prompts PEEP escalation. Persistently elevated peak pressures (≥ 35 cmH_2O), hypercarbia ($PaCO_2 \geq 80$), or hypoxemia (inability to wean $Fio_2 \leq 0.60$ despite increased PEEP) prompted consideration for changing the mode of ventilation or escalating to extracorporeal membrane oxygenation (ECMO). Actual transition or use of ancillary therapy was left to the discretion of the attending physician.

Determination of cause of ARDS

Etiology of ARDS was determined prospectively, most commonly by concurrent chart abstraction, or in unclear cases, by querying the treating PICU attending on the likely etiology. Remaining uncertain cases were adjudicated by a three-person team of PICU physicians, with discussion until unanimous consent. Infectious pneumonia, aspiration, drowning, pulmonary contusion, and smoke inhalation were considered direct ARDS; non-pulmonary sepsis, non-thoracic trauma, non-cardiogenic shock, transfusion-related acute lung injury (TRALI), and pancreatitis were indirect. Infectious pneumonia and non-pulmonary sepsis were considered infectious ARDS; all other etiologies were non-infectious.

Equations and definitions

Oxygenation was measured using Pao_2/Fio_2 or OI (mean airway pressure [mPaw] $\times$ $Fio_2 \times 100$)/Pao_2). Vasopressor score [13] was: dopamine (μg/kg/min) $\times 1$ + dobutamine (μg/kg/min) $\times 1$ + epinephrine (μg/kg/min) $\times 100$ + norepinephrine (μg/kg/min) $\times 100$ + phenylephrine (μg/kg/min) $\times 100$ + vasopressin (U/kg/min) $\times 10{,}000$ + milrinone (μg/kg/min) $\times 10$. Non-pulmonary organ failures were identified using accepted definitions in children [14]. The designation "immunocompromised" required presence of an immunocompromising diagnosis (oncologic, immunologic, rheumatologic, or transplant) and active immunosuppressive chemotherapy, or a congenital immunodeficiency [10, 15]. Severity of illness score used was the Pediatric Risk of Mortality (PRISM) III at 12 h.

Outcomes

Primary outcome was PICU mortality. Secondary outcomes were (1) a composite of either ECMO or PICU mortality (ECMO/mortality) and (2) probability of extubation. Cause of death was classified as either hypoxemia, multisystem organ failure (MSOF), or neurologic, as we have done previously [10, 16]. Duration of ventilation and ventilator-free days (VFD) at 28 days were also reported. All mention of "ventilation" implies invasive ventilation; non-invasive support was not counted. "Day 1" was initiation of invasive ventilation. Liberation from ventilation ≥ 24 h defined duration of ventilation. Patients requiring re-initiation of invasive ventilation had the extra days counted towards total ventilator days. VFD was determined by subtracting total ventilator days from 28 in survivors. Patients with ≥ 28 ventilator days and PICU non-survivors were assigned VFD = 0.

Statistical analysis

Analyses were performed using Stata 14.2 SE. Data are expressed as percentages or medians [interquartile range] and analyzed using Wilcoxon rank-sum or Fisher exact

tests. Select univariate analyses are also presented using survival curves analyzed using log-rank tests.

To determine risk factors for mortality, we tested univariate association with mortality on the whole cohort, then repeated the analysis after stratifying by direct or indirect ARDS, and separately by infectious or non-infectious. Variables associated with mortality in univariate analysis ($p < 0.1$) were entered into a logistic regression model. We considered a Cox proportional hazard model rather than a logistic for determining independent predictors of mortality. However, variable inspection demonstrated that not all variables (specifically, immunocompromised status) met the proportional hazard assumption, thus precluding a Cox model. Therefore, we opted for the logistic model, which required fewer assumptions of our data. Because of collinearity between oxygenation and ventilator variables at ARDS onset and 24 h, only OI at 24 h was modeled, as it incorporates both oxygenation and ventilator pressures, and because we and others have demonstrated 24-h oxygenation is a superior prognostic metric of ARDS severity [10, 17–19]. We then used a manual backward stepwise process by removing the term with the highest p value, and compared models using likelihood ratio (LR) testing and the akaike information criterion (AIC) [20]. This continued until no further variables could be removed and AIC was minimized. To evaluate whether variables had differential effects based on ARDS subtype, we then introduced interaction terms (separately) for indirect ARDS and for non-infectious ARDS, and tested terms against each variable. After interaction testing, we constructed the final model (with interactions) and compared with simpler models using LR testing and AIC. Multicollinearity of the model was assessed using variance inflation factors. Model fit was assessed using the Hosmer–Lemeshow test. Additional models were identically constructed to test the outcome ECMO/mortality, and for subgroup analyses.

We also tested for variables associated with probability of extubation given the competing risk of death using Fine and Gray regression [21], wherein extubation is considered the primary outcome and death the competing event. This provides a subdistribution hazard ratio (SHR) for probability of extubation accounting for competing risk of death. By censoring outcomes at 28 days, this outcome becomes analogous to VFD at 28 days. The multivariate model was constructed by manual backward stepwise variable selection minimizing AIC and testing for significance of interaction terms using the Wald test. The proportional hazard assumption was assessed by testing for interaction with a time-dependent covariate.

Classification and regression tree analysis

To provide a tool to visualize and implement mortality prediction, we performed classification and regression tree (CART) analysis (Salford Predictive Modeler v8.2; Salford Systems, San Diego, CA) using variables from the final model. Terminal nodes that did not improve classification by class probability were pruned. The model was developed with tenfold cross-validation, and area under the receiver operating characteristic (AUROC) curve calculated.

Results

Description of the cohort

During the study period, 544 children with ARDS were included (Table 1). Direct lung injury accounted for 384 (71%) of cases, of which 282 (73% of 384) were infectious. Infection accounted for 404 (74%), of which 282 (70% of 404) were direct. Thirty-nine subjects required adjudication for determination of ARDS etiology, most commonly (24 cases) differentiating between infectious pneumonia and non-pulmonary sepsis. Non-survivors ($n = 93$, 17%) were older, had greater severity of illness, worse oxygenation, and were more commonly immunocompromised. Berlin (Fig. 1) demonstrated better discrimination and calibration of outcome at 24 h, relative to ARDS onset, whereas PALICC was similar at both timepoints (Supplementary Fig. 1).

Direct versus indirect ARDS

Subjects with indirect ARDS were older, had greater severity of illness, and were more commonly immunocompromised than those with direct ARDS (Supplementary Table 1). Patients with indirect ARDS had better oxygenation (both Pao_2/Fio_2 and OI) at ARDS onset, and a lower OI at 24 h. Inhaled nitric oxide, continuous neuromuscular blockade, and non-conventional ventilation were more common for direct ARDS. Non-survivors of indirect ARDS were more likely to die from MSOF. In univariate analysis, greater severity of illness and immunocompromised status were associated with mortality in both direct and indirect ARDS (Supplementary Table 2). Worse OI and higher ventilator pressures at both ARDS onset and at 24 h were associated with mortality in direct ARDS, whereas only oxygenation and ventilator pressures at 24 h were associated with mortality in indirect ARDS.

Infectious versus non-infectious ARDS

Subjects with non-infectious ARDS were older, had greater severity of illness, and were less likely to have any co-morbidities than those with infectious ARDS (Supplementary Table 3). Subjects with non-infectious ARDS had improved oxygenation 24 h after ARDS onset, and a shorter duration of ventilation in survivors. However, non-infectious ARDS subjects had higher mortality (24%) relative to infectious (15%, $p = 0.013$), and were more likely to die from neurologic causes. Severity of illness was associated with mortality for both infectious and non-infectious ARDS (Supplementary Table 4).

Table 1 Characteristics of the cohort stratified by survival status

Variables	All patients ($n=544$)	Survivors ($n=451$)	Non-survivors ($n=93$)	p value
Age (years)	4.6 [1.5, 12.2]	4.1 [1.4, 11.4]	7.2 [3.2, 14.3]	< 0.001
Female (%)	239 (44)	202 (45)	37 (40)	0.422
Severity of illness				
PRISM III at 12 h	11 [5, 18]	9 [4, 15]	19 [12, 31]	< 0.001
Non-pulmonary organ failures	2 [1, 3]	1 [1, 2]	3 [2, 4]	< 0.001
Vasopressor score	10 (3, 20)	8 [3, 17]	20 [8, 55]	< 0.001
Co-morbidities (%)				
None	220 (40)	186 (41)	34 (37)	0.419
Prematurity	68 (13)	67 (15)	2 (2)	< 0.001
Genetic syndrome	88 (16)	79 (18)	10 (11)	0.124
Epilepsy	79 (15)	75 (17)	6 (6)	0.010
Malignancy	75 (14)	52 (12)	23 (25)	0.002
Immunocompromised	106 (19)	65 (14)	41 (44)	< 0.001
Cause of ARDS (%)				
Direct (%)	384 (71)	326 (72)	58 (62)	0.061
Infectious (%)	404 (74)	345 (77)	59 (63)	0.013
Cause of ARDS (%)				0.008
Infectious pneumonia	282 (52)	250 (55)	32 (34)	
Aspiration pneumonia	69 (13)	54 (12)	15 (17)	
Drowning	15 (3)	9 (2)	6 (6)	
Thoracic trauma/contusion	13 (2)	10 (2)	3 (3)	
Smoke inhalation	5 (1)	3 (1)	2 (2)	
Non-pulmonary sepsis	122 (22)	95 (21)	27 (29)	
Non-thoracic trauma	22 (4)	17 (4)	5 (5)	
Non-cardiogenic shock	12 (2)	10 (2)	2 (2)	
TRALI	3 (0.6)	2 (0.4)	1 (1)	
Pancreatitis	1 (0.2)	1 (0.2)	0	
ARDS onset				
PaO_2/FIO_2	158 [105, 218]	162 [113, 220]	135 [71, 206]	< 0.001
OI	10.2 [7, 17.7]	10 [7, 15.8]	15.4 [7.3, 25.8]	< 0.001
PIP (cmH_2O)	30 [26, 35]	30 [26, 35]	31 [28, 38]	< 0.001
PEEP (cmH_2O)	10 [8, 12]	10 [8, 12]	10 [8, 12]	< 0.001
ΔP (cmH_2O)	21 [16, 25]	20 [16, 24]	21 [17, 26]	< 0.001
V_T (mL/kg)	7.5 [6.6, 8.4]	7.4 [6.5, 8.4]	7.7 [6.8, 8.3]	< 0.001
Berlin category at ARDS onset				0.001
Mild	175 (32)	148 (33)	27 (29)	
Moderate	245 (45)	214 (47)	31 (33)	
Severe	124 (23)	89 (20)	35 (38)	
PaO_2/FIO_2	223 [158, 283]	231 [170, 292]	182 [106, 251]	< 0.001
OI	6.9 [4.8, 12]	6.6 [4.7, 10.8]	9.3 [5.7, 23.8]	< 0.001
PIP (cmH_2O)	27 [24, 32]	27 [23, 31]	30 [25, 35]	< 0.001
PEEP (cmH_2O)	10 [8, 10]	10 [8, 10]	10 [8, 12]	< 0.001
ΔP (cmH_2O)	18 [14, 22]	17 [14, 22]	20 [15, 24]	< 0.001
V_T (mL/kg)	7.3 [6.5, 8.1]	7.3 [6.5, 8.1]	7.1 [6.3, 8]	< 0.001
Berlin category at 24 h				< 0.001
Resolved	109 (20)	97 (22)	12 (13)	
Mild	206 (38)	183 (41)	23 (26)	
Moderate	174 (32)	142 (31)	32 (36)	
Severe	51 (9)	29 (6)	22 (25)	

Table 1 continued

Variables	All patients ($n=544$)	Survivors ($n=451$)	Non-survivors ($n=93$)	p value
Ancillary therapies (%)				
Inhaled nitric oxide	201 (37)	148 (33)	53 (57)	< 0.001
Neuromuscular blockade	256 (47)	214 (47)	42 (45)	0.733
Corticosteroids	297 (55)	231 (51)	66 (71)	0.001
Alternative ventilator modes	168 (31)	136 (30)	32 (34)	0.460
Extracorporeal support	22 (4)	18 (4)	4 (4)	0.779

OI oxygenation index, *PRISM* pediatric risk of mortality, *PEEP* positive end expiratory pressure, *PIP* peak inspiratory pressure, *ΔP* PIP minus PEEP, *TRALI* transfusion associated acute lung injury, V_T tidal volume

Oxygenation and ventilator pressures at ARDS onset were associated with mortality in infectious ARDS, while only OI and tidal volume at onset were associated with mortality in non-infectious ARDS. By 24 h, oxygenation and ventilator pressures were only associated with mortality in infectious ARDS. Immunocompromised status and presence of a malignancy was similarly only associated with mortality in infectious ARDS.

Independent risk factors between ARDS subtypes

We performed multiple logistic regression using a manual backward selection process. The model without any interaction terms (Supplementary Table 5) showed mortality was associated with PRISM III, number of non-pulmonary organ failures, immunocompromised status, direct ARDS etiology, and higher OI at 24 h. We then introduced interaction terms (separately) for indirect ARDS (reference: direct) and non-infectious ARDS (reference: infectious), testing for interactions with each variable in the model. Immunocompromised status had a significant interaction with both indirect ARDS and with non-infectious ARDS (both $p<0.05$). Inclusion of both interaction terms improved model fit ($p=0.005$ for LR test relative to simpler model without interaction terms), resulting in the final model (Table 2). Immunocompromised status had a differential effect on infectious versus non-infectious ARDS, with an association between immunocompromised status and increased mortality only seen in infectious ARDS. Within infectious ARDS, there was a larger effect of immunocompromised status on direct ARDS, relative to indirect (Table 2, Fig. 2). When constructing models for the composite endpoint ECMO/mortality (Supplementary Table 6) and probability of extubation (Supplementary Table 7), we again saw an interaction between infectious/non-infectious ARDS and immunocompromised status, but direct/indirect was no longer retained.

Subgroup analyses

Because OI may perform differently in non-conventional ventilation, we repeated our analysis restricted to subjects only on conventional ventilation (Supplementary Table 8). We again demonstrated that immunocompromised status had a differential effect on infectious versus non-infectious ARDS. When we excluded subjects dying of neurologic causes (Supplementary Table 9), the final model retained organ failures, immunocompromised status, and OI at 24 h as associated with PICU mortality. Finally, we constructed models predicting outcomes in immunocompetent subjects (Supplementary Table 10). PRISM score, organ failures, and non-infectious ARDS were associated with mortality and ECMO/mortality, while OI at 24 h was also associated with ECMO/mortality. Increasing organ failures and OI at 24 h were associated with lower probability of extubation, while indirect ARDS was associated with higher probability of extubation.

CART analysis

To visualize and implement mortality prediction, we performed CART analysis using the variables in Table 2. The final tree (Fig. 3) retained non-pulmonary organ failure, OI at 24 h, infectious/non-infectious ARDS, and immunocompromised status. There were five terminal nodes: one low-risk (green, 2% mortality), one intermediate (blue, 8% mortality), and three high-risk (red, $\geq$ 33% mortality). This model had AUROC of 0.81 (95% CI 0.76–0.86) for discriminating PICU mortality. Consistent with the regression model, infectious ARDS had a subsequent branch point for immunocompromised status, whereas non-infectious ARDS did not.

Discussion

Clinical characteristics differ between direct and indirect ARDS, as well as between infectious and non-infectious ARDS. While severity of illness predicted mortality consistently across all subtypes, immunocompromised status was differentially associated with mortality in infectious versus non-infectious ARDS. This may be due to the higher prevalence of neurologic deaths in non-infectious ARDS. Traditional predictors of mortality, such as

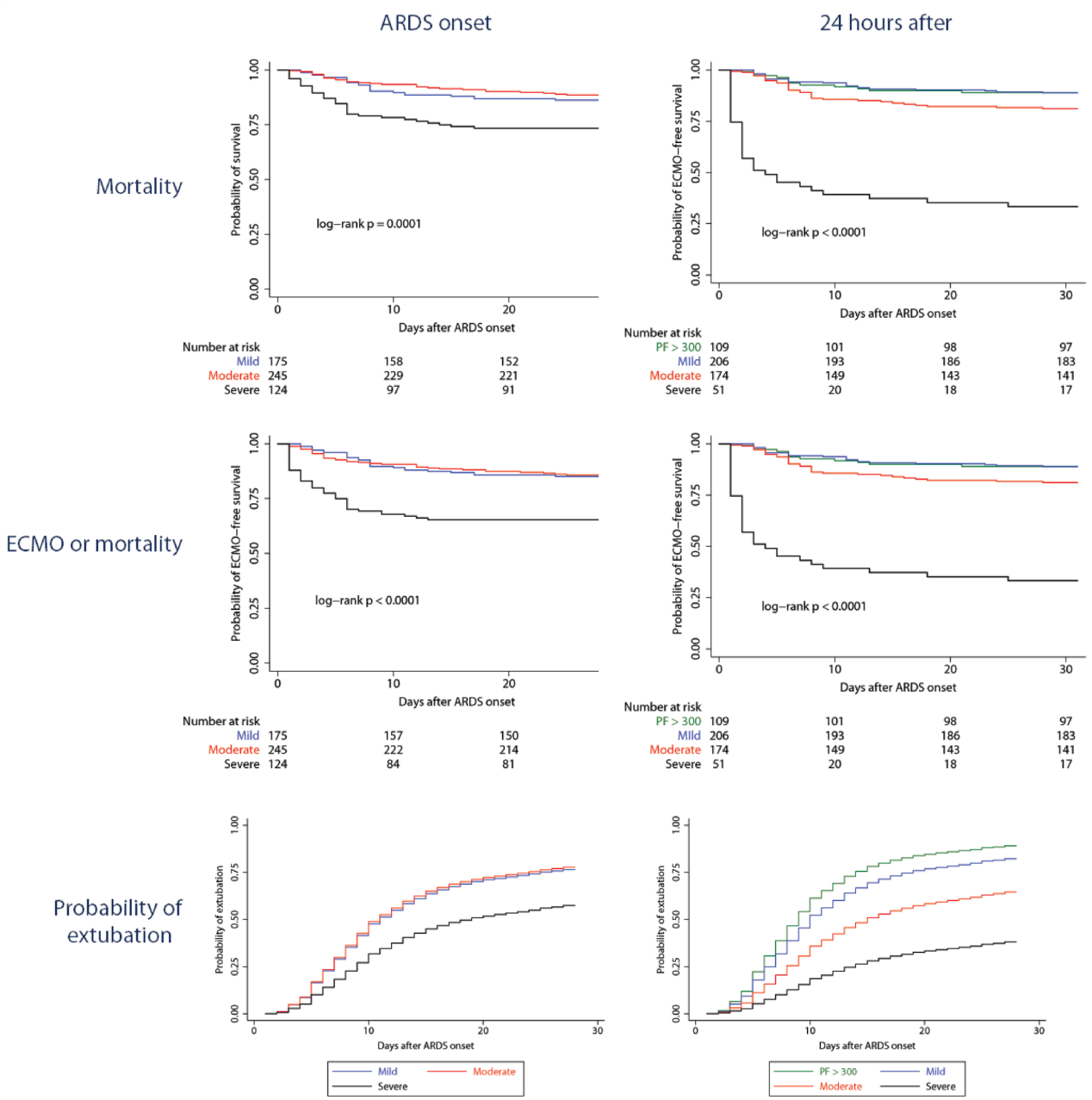

Fig. 1 Kaplan–Meier survival curves for the outcomes of survival, ECMO-free survival, or probability of extubation given the competing risk of death, stratified by Berlin severity categories, at ARDS onset and at 24 h. All curves are censored at 28 days. At ARDS onset, there is overlap of mild (blue) and moderate (blue) categories, whiles severe (black) demonstrates worse survival, ECMO-free survival, and lower probability of extubation. By 24 h, there is improved separation of the categories for all outcomes, with residual overlap between resolved (green) and mild (red) ARDS

immunocompromised status and oxygenation, were only associated with mortality in infectious ARDS. This is the first description of associations between clinical characteristics and mortality in different subtypes of pediatric ARDS.

Direct and indirect ARDS present differently, with higher severity of illness and more immunocompromised subjects in indirect ARDS, and worse oxygenation in direct ARDS.

After adjustment, the direct/indirect designation was not associated with mortality. Infectious and non-infectious ARDS also differed clinically: non-infectious ARDS had higher severity of illness, better oxygenation, and higher mortality. After adjustment for confounders,

Table 2 Final model for PICU mortality with both interaction terms included

Variable	aOR (95% CI)	*p* value
PRISM III	1.05 (1.02–1.09)	0.001
Organ failures	2.27 (1.68–3.06)	< 0.001
Indirect ARDS	0.75 (0.31–1.81)	0.525
Non-infectious ARDS	2.34 (1.09–5.04)	0.030
Immunocompromised		
Direct/infectious	**12.81 (4.87–33.71)**	**< 0.001**
Indirect/infectious	**3.27 (1.22–8.77)**	**0.019**
Direct/non-infectious	1.71 (0.43–6.73)	0.446
Indirect/non-infectious	0.43 (0.11–1.78)	0.247
Interaction terms		
Direct/indirect*immunocompromised	0.25 (0.07–0.91)	0.036
Infectious/non-infectious*immunocompromised	0.13 (0.03–0.55)	0.005
OI 24 h after ARDS onset	1.02 (1.00–1.04)	0.037

OI oxygenation index, *PRISM* pediatric risk of mortality

non-infectious ARDS retained association with mortality (odds ratio 2.34, 95% CI 1.09–5.04, $p = 0.030$).

Severity of illness as measured by PRISM III and organ failures was consistently associated with mortality in all subtypes. OI at 24 h was also associated with mortality in the full model, as previously shown [22], but not when restricted to non-infectious ARDS. It is unclear whether worse OI reflects a pulmonary-specific risk factor, or whether it is the pulmonary manifestation of MSOF. The higher mortality in non-infectious ARDS, despite improved oxygenation and shorter ventilator duration in survivors, confirms that subjects were likely dying from causes other than severe ARDS, including neurologic etiologies, for which OI at 24 h is not a risk factor.

Immunocompromised status was independently associated with mortality with evidence of effect modification. Immunocompromised status was not a predictor of mortality in non-infectious ARDS in either univariate or multivariate analysis. This is the first study to suggest that non-infectious pediatric ARDS has different

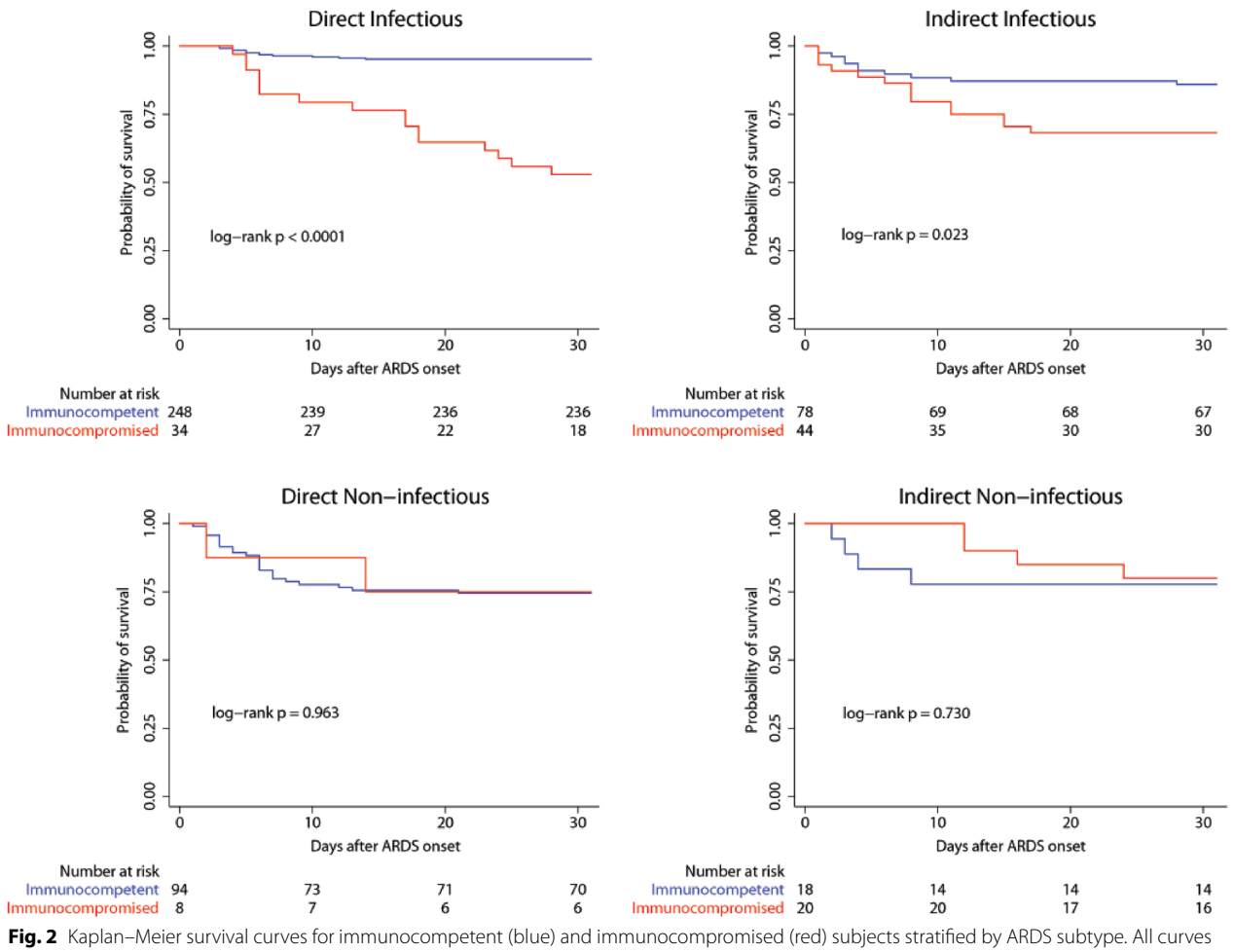

Fig. 2 Kaplan–Meier survival curves for immunocompetent (blue) and immunocompromised (red) subjects stratified by ARDS subtype. All curves are censored at 28 days

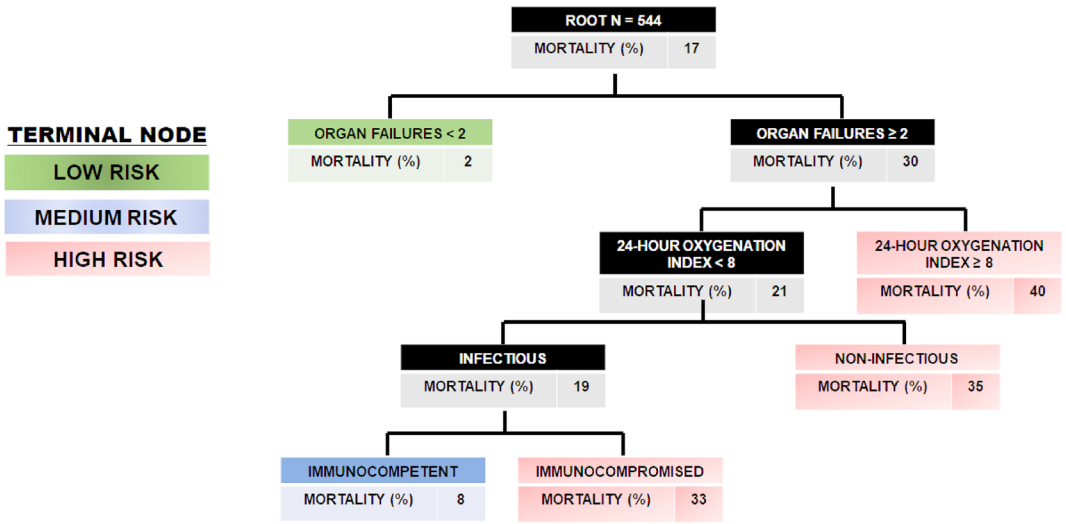

Fig. 3 Decision tree for mortality constructed from variables retained in the final model using classification and regression tree (CART) methodology. The tree contains mortality at each decision point and the decision rules. The final model resulted in a tree with five terminal nodes: one low-risk (green), one intermediate risk (blue), and three high-risk (red)

outcome predictors. Previous cohorts have suggested immunocompromised status as a predictor of mortality [8, 23]. Given that the most common etiologies in those cohorts, as in ours, were pneumonia and non-pulmonary sepsis, it is possible that over-representation of infectious ARDS, and particularly pneumonia, made apparent an association of immunocompromised status and mortality for the entire cohort. Our results are consistent with previous studies but are large enough to test for differential effects of immunocompromised status within subtypes. The largest effect of immunocompromised status on mortality was seen in direct infectious ARDS (i.e., pneumonia), which accounts for the majority of ARDS etiologies in most cohorts [7, 8, 10, 18]. The interaction between immunocompromised status and infectious/non-infectious ARDS disappeared when excluding subjects who died from neurologic causes, suggesting that the lack of association between immunocompromised status and mortality in non-infectious ARDS is due to a higher proportion of severe neurologic failure among non-infectious ARDS, making the presence of an immunocompromising condition less relevant for mortality. Importantly, the differential impact of immunocompromised status on infectious versus non-infectious ARDS was confirmed in CART analysis. This is significant as CART is a non-parametric methodology which performs automatic variable selection and is often used to "discover" interactions between variables de novo. CART analysis retained infectious versus non-infectious ARDS and immunocompromised status and discovered an interaction effect between these variables. Direct versus indirect ARDS was not retained in the CART analysis, highlighting the greater significance of the infectious categorization, rather than the direct/indirect designation, for short-term mortality prediction.

Differences in mortality predictors between infectious and non-infectious etiologies support the existence of subtypes within pediatric ARDS. In adults, emerging literature suggests that different ARDS subtypes exist, and potentially impact outcomes [1, 3, 6, 24–27]. Recently, adult ARDS subtypes have been identified using latent class analysis of clinical and biochemical variables [6, 24], broadly corresponding to hypo- and hyperinflammatory phenotypes. These subtypes have differential responses to PEEP [6] and fluid management [24]. Comparable analyses have not been performed in children, limited by lower prevalence of pediatric ARDS, smaller available cohorts, fewer clinical trials, and lower mortality [10, 28, 29]. Future pediatric ARDS trials should stratify by type of lung injury, or pre-specify post hoc analyses, to account for differential effects of intervention between subtypes. Our data suggest that infectious or non-infectious ARDS is a more important stratification, relative to direct or indirect ARDS.

Our study has limitations. The single-center nature limits generalizability, although ARDS etiologies, severity, and mortality were comparable to others [7, 8, 18, 30, 31]. We did not screen using Berlin or PALICC definitions as these were not available at the start of our study, although all subjects met Berlin criteria. Our results are not generalizable to subjects with unilateral infiltrates, which are allowed under PALICC. Similarly, as we did

not screen using Spo_2, we may have missed subjects lacking arterial access, as well as explicit Spo_2-based classification allowed by PALICC. It is possible that a cohort screened using more modern definitions of ARDS would result in a model with different predictors. Only recorded variables were tested in the regression model, and it is possible that relevant predictors went unmeasured. However, our data collection focused on variables with prior associations with mortality. We were not able to perform the commonly accepted Cox regression because of limitations in our data, which precludes some information regarding the shape of the survival curves and time to death. Despite the size of the cohort, division into subtypes results in smaller sample sizes, with as few as 34 deaths in non-infectious ARDS, limiting identification of factors associated with mortality in subgroups. However, the main conclusion of a differential effect of immunocompromised status in infectious versus non-infectious ARDS is consistent throughout all analyses. Finally, as there is no gold standard for assigning ARDS etiology, it is possible that some subjects were misclassified.

Our study has several strengths. This is a large, prospective cohort from a tertiary PICU with detailed data collection, and the first study powered to address the existence of ARDS subtypes. Etiologies were assigned nearly in real-time, with a protocolized procedure for uncertain cases. The dense, registry-style phenotyping allowed us to assess the association between mortality and several relevant variables. We tested multiple outcomes, including a composite of ECMO/mortality and probability of extubation, and provided an operational tree to stratify mortality risk. While our results require external validation, they provide a framework for future observational and interventional studies in pediatric ARDS.

Conclusions

In pediatrics, direct and indirect ARDS have different clinical characteristics, but similar outcomes and similar predictors of mortality. By contrast, infectious and non-infectious ARDS demonstrate differences in clinical characteristics, mortality, and predictors of mortality. Immunocompromised status, a traditional predictor of mortality, is only applicable to infectious ARDS. Infectious and non-infectious ARDS have distinct features differentially affecting risk prediction and outcome, which should be accounted for in future studies.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5286-6) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

Dr. Yehya's institution receives funding from the NIH (K12-HL-136688). Dr. Thomas reports personal fees from Therabron and Carefusion, all outside of the submitted work.

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