Original Article
Yonsei Med J 2023 Jun;64(6):384-394
https://doi.org/10.3349/ymj.2022.0653
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Radiologic Assessment of Lung Edema Score as a Predictor of Clinical Outcome in Children with Acute Respiratory Distress Syndrome

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Purpose: The radiographic assessment of lung edema (RALE) score enables objective quantification of lung edema and is a valuable prognostic marker of adult acute respiratory distress syndrome (ARDS). We aimed to evaluate the validity of RALE score in children with ARDS.

Materials and Methods: The RALE score was measured for its reliability and correlation to other ARDS severity indices. ARDS-specific mortality was defined as death from severe pulmonary dysfunction or the need for extracorporeal membrane oxygenation therapy. The C-index of the RALE score and other ARDS severity indices were compared via survival analyses.

Results: Among 296 children with ARDS, 88 did not survive, and there were 70 ARDS-specific non-survivors. The RALE score showed good reliability with an intraclass correlation coefficient of 0.809 [95% confidence interval (CI), 0.760–0.848]. In univariable analysis, the RALE score had a hazard ratio (HR) of 1.19 (95% CI, 1.18–3.11), and the significance was maintained in multivariable analysis adjusting with age, ARDS etiology, and comorbidity, with an HR of 1.77 (95% CI, 1.05–2.91). The RALE score was a good predictor of ARDS-specific mortality, with a C-index of 0.607 (95% CI, 0.519–0.695).

Conclusion: The RALE score is a reliable measure for ARDS severity and a useful prognostic marker of mortality in children, especially for ARDS-specific mortality. This score provides information that clinicians can use to decide the proper time of aggressive therapy targeting severe lung injury and to appropriately manage the fluid balance of children with ARDS.

Key Words: Acute respiratory distress syndrome, children, critical care outcome, mechanical ventilator, mortality prediction

INTRODUCTION

Acute respiratory distress syndrome (ARDS) in children is different from that of adults in terms of the developmental stage, leading to the consensus on a new definition outlined by the Pediatric Acute Lung Injury Consensus Conference (PALICC).[1-3] While various measures are available to gauge the severity of ARDS, according to the PALICC definition, the oxygenation index (OI) is mainly used to define and categorize ARDS severity.[1,4-6] As OI represents hypoxia in ARDS, indices that measure other aspects of ARDS, such as ventilatory ratio (VR) and lung compliance, have been validated to characterize ARDS severity, and predict clinical outcomes.[5,7,8]

Lung edema, a major component of ARDS pathophysiology, is also considered a target to be measured.[9] In attempt to quantify lung edema using chest radiographs, the radiographic assessment of lung edema (RALE) score was developed, and its

Received: February 27, 2023 **Revised:** March 27, 2023
Accepted: March 28, 2023 **Published online:** May 18, 2023
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•The authors have no potential conflicts of interest to disclose.

credibility as a representation of lung edema has been proven.[10] However, while its association with clinical outcomes has been validated for adults, very few studies have validated the RALE score in children.[11] Considering the differences in pathophysiology and epidemiologic characteristic of ARDS between children and adults, and the high inter-rater variability in the assessment of chest radiographs of pediatric ARDS,[12] a re-evaluation of the RALE score for children with ARDS is warranted.

This study aimed to evaluate the reliability of the RALE score for children with ARDS. Additionally, we validated the RALE score as a predictor of mortality using survival analysis and compared its performance with that of other indices of ARDS severity.

MATERIALS AND METHODS

Subjects

We included children aged below 18 years, admitted to medical intensive care units (ICUs) between June 2009 and March 2021, who met the PALICC definition of pediatric ARDS and were treated with mechanical ventilation.[1] Electrical medical records of each subject were reviewed, and basic demographics including age, sex, severity of ARDS based on OI, ARDS etiology, comorbidity were recorded. For each patient, the ventilator settings at the time of ARDS onset and arterial blood gas analysis (ABGA) results, and chest radiographs that first met the PALICC criteria were identified within 7 days of known clinical insult or worsening respiratory symptoms.[1] This study was approved by the Institutional Review Board of the Institutional Review Board of Severance Hospital (IRB No. 4-2022-1452), and the requirement for informed consent was waived.

Outcome variables

The main prognostic outcomes of overall mortality and ARDS-specific mortality were assessed. Overall mortality was based on the all-cause in-hospital mortality. For determining ARDS-specific mortality, the main organ system that caused death was identified using an assessment method for adult ARDS, described in a previous study,[13] that was adapted for children. Briefly, each non-survivor's organ dysfunctions were classified to eight organ systems, and the presence of severe or irreversible dysfunction was confirmed (Supplementary Tables 1 and 2, only online). Then, using an algorithm (Supplementary Table 3, only online), the cause of death in terms of organ system was determined. We defined ARDS-specific mortality to include children who had pulmonary dysfunction as the cause of death and those who received extracorporeal membrane oxygenation (ECMO).

ARDS severity index

The RALE score of a radiograph was determined according to the method described in a previous study of adult ARDS.[4] As described, the lung fields were divided into four quadrants, using a line connecting the spinal process of vertebral column and a line perpendicular to the spine passing the first branch of the left main bronchus. Then, a consolidation score and a density score were assigned to each quadrant. The consolidation score measures the extent of opacity, ranging from 0 (no opacity) to 4 (opacity covering >75% of the quadrant), while density score measures the general density of opacity, ranging from 1 (hazy) to 3 (dense). The product of two scores is then calculated for each quadrant, from which the final RALE score is obtained by summing the scores of four quadrants. Two clinicians reviewed each chest radiograph of ARDS onset separately; then, the average of the two scores was considered the final RALE score. To account for the cases in which the scores of reviewers were significantly discrepant, we assessed the distribution of the discrepancy; and for cases in which the difference was larger than 1.5× interquartile range (IQR), the RALE score was decided by a third reviewer. The average of two scores close to each other among the three reviewers was considered the final RALE score in these cases.[14]

The other ARDS severity indices we assessed and compared with the RALE score included the following: PaO_2/FIO_2 (PF) ratio, OI, VR, and dynamic lung compliance (Cdynamic). All indices were calculated from the ABGA results and ventilator setting of ARDS onset. Further description of how we calculated these indices is given below:

- OI was calculated as $(FIO_2/PaO_2)\times$mean airway pressure $\times 100$.[1]
- VR was calculated as (measured minute ventilation×measured $PaCO_2$)/(predicted minute ventilation×ideal $PaCO_2$). We used the 10th, 50th and 90th percentile respiratory rate of each child's age as reference and used a predicted tidal volume of 7 mL/kg per weight to calculate predicted minute ventilation; 37.5 mm Hg was considered the ideal $PaCO_2$.[7,15]
- Cdynamic was calculated as tidal volume/(Peak Inspiratory Pressures–Positive End-Expiratory Pressure).[16]

Furthermore, the Pediatric Risk of Mortality-3 (PRISM-3) and the Pediatric Index of Mortality-3 (PIM-3), which are prognostic composite score systems for mortality, were also compared with the ARDS indices.[17]

Statistical analysis

We compared the demographics between the survivors and non-survivors and between ARDS-specific survivors and ARDS-specific non-survivors using an independent two sample t-test for continuous variables with normal distribution, Mann-Whitney U test for those without normal distribution, and chi-square test for categorical variables. To assess the reliability of the RALE score across the initial two independent reviewers, the intraclass correlation coefficient (ICC)[18] was calculated, and Bland–Altman plots[19] were used to visualize the agreement

between the two reviewers. We analyzed the correlation between the RALE score and other severity indices using the Pearson correlation coefficient and visualized using the correlation matrix. The overall and ARDS-specific mortality were compared across quartiles of RALE scores and other severity indices by linear-by-linear association test.

We decided the cut-off RALE score for overall and ARDS-specific mortality by using the Contal and O'Quigley method,[20] and categorized the subjects into high and low RALE score groups. Survival curves were determined by the Kaplan–Meier method, and the differences in the overall and ARDS-specific survival between the high and low RALE score groups were analyzed using the log-rank test. We compared the demographics and other severity indices between high and low RALE score groups and selected the confounding variables that did not show significant difference, with $p<0.1$ for selecting proper confounding variables. We used Cox proportional hazard regression models to determine the hazard ratios (HRs). The selected confounding variables with $p<0.1$ on univariable analysis were included in the multivariable analysis.

To compare the capacities of the RALE score and of other severity indices, we calculated the C-index [95% confidence interval (CI)] and compared the values of the RALE score and other severity indices.[21] We fit the Cox proportional hazard regression models with restricted cubic splines for each severity index to determine whether a more complex, nonlinear relationship existed between the severity indices and the outcome. We used IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA), SAS version 9.4 (SAS Institute, Cary, NC, USA), and R statistical package (R version 4.1.3.; www.R-project.org) for all analyses.

RESULTS

Clinical characteristics

We included 296 children diagnosed with ARDS, 208 of whom survived while 88 did not. Among the non-survivors, the causes of death for 28 children were dysfunctions of organ systems other than the respiratory system. Excluding these patients while including 10 survivors who required ECMO, 70 were ARDS-specific non-survivors, compared to 198 ARDS-specific survivors, who survived without the use of ECMO. We compared the clinical characteristics of overall survivors vs. non-survivors and ARDS-specific survivors vs. ARDS-specific non-survivors (Table 1). The median age of all participants was 4.0 years (IQR, 1.4–11.3). There were 126 (42.6%) females. The overall mortality increased as the severity increased from mild and moderate to severe ARDS (linear-by-linear association analysis, $p<0.001$), and ARDS-specific mortality showed a similar trend (linear-by-linear association analysis, $p<0.001$).

Among different ARDS etiologies, infectious pneumonia was

Table 1. Demographics of the Study Population

	Total (n=296)	Survivors (n=208)	Non-survivors (n=88)	*p* value*	ARDS-specific survivors (n=198)	ARDS-specific non-survivors§ (n=70)	*p* value†
Age, yr	4.0 (1.4–11.3)	3.6 (1.1–10.4)	6.1 (2.2–13.8)	0.001	3.5 (1.0–10.3)	6.1 (2.2–12.3)	0.004
Sex, female	126 (42.6)	95 (45.7)	31 (35.2)	0.097	91 (46.0)	24 (34.3)	0.090
PALICC grade				<0.001			<0.001
Mild	124 (41.9)	103 (49.5)	21 (23.9)		105 (51.0)	12 (17.1)	
Moderate	112 (37.8)	79 (38.0)	33 (37.5)		73 (36.9)	28 (40.0)	
Severe	60 (20.5)	26 (12.5)	34 (38.6)		24 (12.1)	30 (42.9)	
ARDS etiology				<0.001			<0.001
Infectious pneumonia	182 (61.5)	140 (67.3)	42 (47.7)	0.010‡	136 (68.7)	35 (50.0)	0.025‡
Aspiration pneumonia	29 (9.8)	24 (11.5)	5 (5.7)	0.605‡	23 (11.6)	3 (4.3)	0.375‡
Sepsis	56 (18.9)	20 (6.8)	36 (40.9)	<0.001‡	18 (9.1)	26 (37.1)	<0.001‡
Post CPR status	20 (6.8)	16 (7.7)	4 (4.5)	>0.999‡	7 (3.5)	1 (1.4)	>0.999‡
Others	9 (3.0)	8 (3.8)	1 (1.1)	>0.999‡	14 (7.1)	5 (7.1)	>0.999‡
Comorbidity				<0.001			<0.001
None	29 (9.8)	25 (12.0)	4 (4.5)	>0.999‡	24 (12.1)	3 (4.3)	0.305‡
Lung or airway diseases	90 (30.4)	66 (22.3)	24 (27.3)	>0.999‡	61 (30.8)	23 (32.9)	>0.999‡
Neurologic disease	83 (28.0)	75 (25.3)	8 (2.7)	0.190‡	73 (36.9)	7 (10.0)	<0.001‡
Hematologic or oncologic disease	64 (21.6)	18 (8.7)	46 (15.5)	0.010‡	17 (8.6)	34 (48.6)	<0.001‡
Genetic disorder or immune deficiency	19 (6.4)	17 (8.2)	2 (0.7)	0.845‡	16 (8.1)	3 (4.3)	>0.999‡
Others	11 (3.7)	7 (3.4)	4 (1.4)	>0.999‡	7 (3.5)	0 (0)	0.555‡

PALICC, Pediatric Acute Lung Injury Consensus Conference; ARDS, acute respiratory distress syndrome; CPR, cardiopulmonary resuscitation.
Data are presented as median (interquartile range) or n (%).
*p value for comparison between survivors and non-survivors; †p value for comparison between ARDS-specific survivors and ARDS-specific non-survivors; ‡p value of the post-hoc analysis using Bonferroni correction; §ARDS-specific non-survivors are children who died of severe pulmonary dysfunction or required extracorporeal membrane oxygenation therapy.

https://doi.org/10.3349/ymj.2022.0653

the most common one, with a prevalence of 61.5% (182 subjects), and the most common comorbidity was baseline lung or airway disease, with a prevalence of 30.4% (90 subjects). The prevalence of infectious pneumonia was found significantly low while that of sepsis was significantly high among the non-survivors and ARDS-specific non-survivors than among their survivor counterparts. In ARDS comorbidity, the prevalence of hematologic and oncologic diseases was significantly high among the non-survivors and ARDS-specific non-survivors than among their survivor counterparts.

Reliability of RALE score and correlation with ARDS severity index

The distribution of the differences in the RALE scores between two initial reviewers was visualized using Bland–Altman plots (Fig. 1). When only the consolidation scores or the density

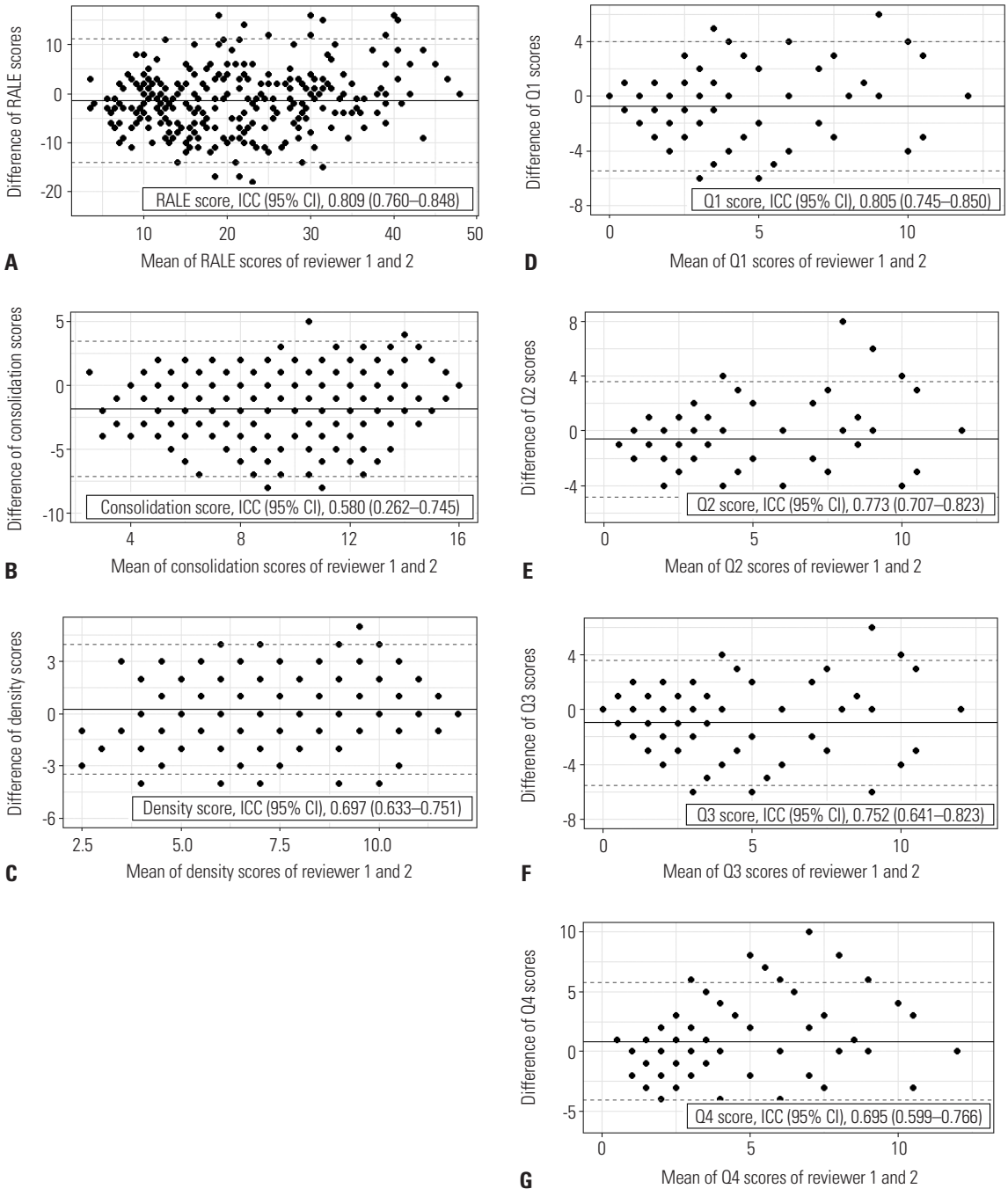

Fig. 1. Inter-observer agreement and reliability assessment using ICC for RALE score (A), consolidation score (B), density score (C), RALE score on quadrant 1 (Q1, D), quadrant 2 (Q2, E), quadrant 3 (Q3, F), and quadrant 4 (Q4, G). RALE, radiographic assessment of lung edema; ICC, intraclass correlation coefficient; CI, confidence interval.

scores were accounted for, the distribution of inter-reviewer difference was rather spread out, with ICCs of 0.580 (95% CI, 0.262–0.745) and 0.697 (95% CI, 0.633–0.761) each. However, when the composite of both consolidation and density was calculated to formulate the RALE score, the ICC increased to 0.809 (95% CI, 0.760–0.848), indicative of good agreement.[22] When the inter-reviewer RALE score difference in each quadrant was evaluated separately, quadrant 4 (Q4) proved to show the least reliable result, with an ICC of 0.695 (95% CI, 0.599–0.766), given that a large portion of left lower lung field can be obscured by the heart.

There were 22 patients whose RALE score differences of the initial reviewers were larger than 1.5×IQR, requiring additional evaluation by the third reviewer. The median value of the differences between the two scores among these patients was 15 (IQR, 12–16). After taking the third reviewer's RALE score into account, the median value of the differences between the two scores used for the final RALE score was 4 (IQR, 2–5).

The Pearson correlation coefficient between ARDS severity indices, scatter plot of each comparison, and histogram of each index are shown as a correlation matrix in Fig. 2. The RALE score was correlated to the PF ratio, OI, VR 50th, and VR 90th with correlation coefficients of 0.34, 0.40, and 0.12, and 0.12 respectively.

Mortality across quartiles of ARDS severity index

Table 2 presents the overall and ARDS-specific mortality rate across the quartiles of different ARDS severity indices. Linear association with both overall mortality and ARDS-specific mortality across the quartiles of RALE score, PF ratio, and OI were statistically significant, showing consistent decrement or increment across quartiles. The linear association of VR 10th, 50th, and 90th quartiles with ARDS-specific mortality was also significant, while its association with overall mortality was not.

Assessment of RALE score in the prediction of pediatric intensive care unit (PICU) mortality

The results of survival analysis with the RALE score for both overall mortality and ARDS-specific mortality are shown in Fig. 3. Between the high RALE score group and low RALE score

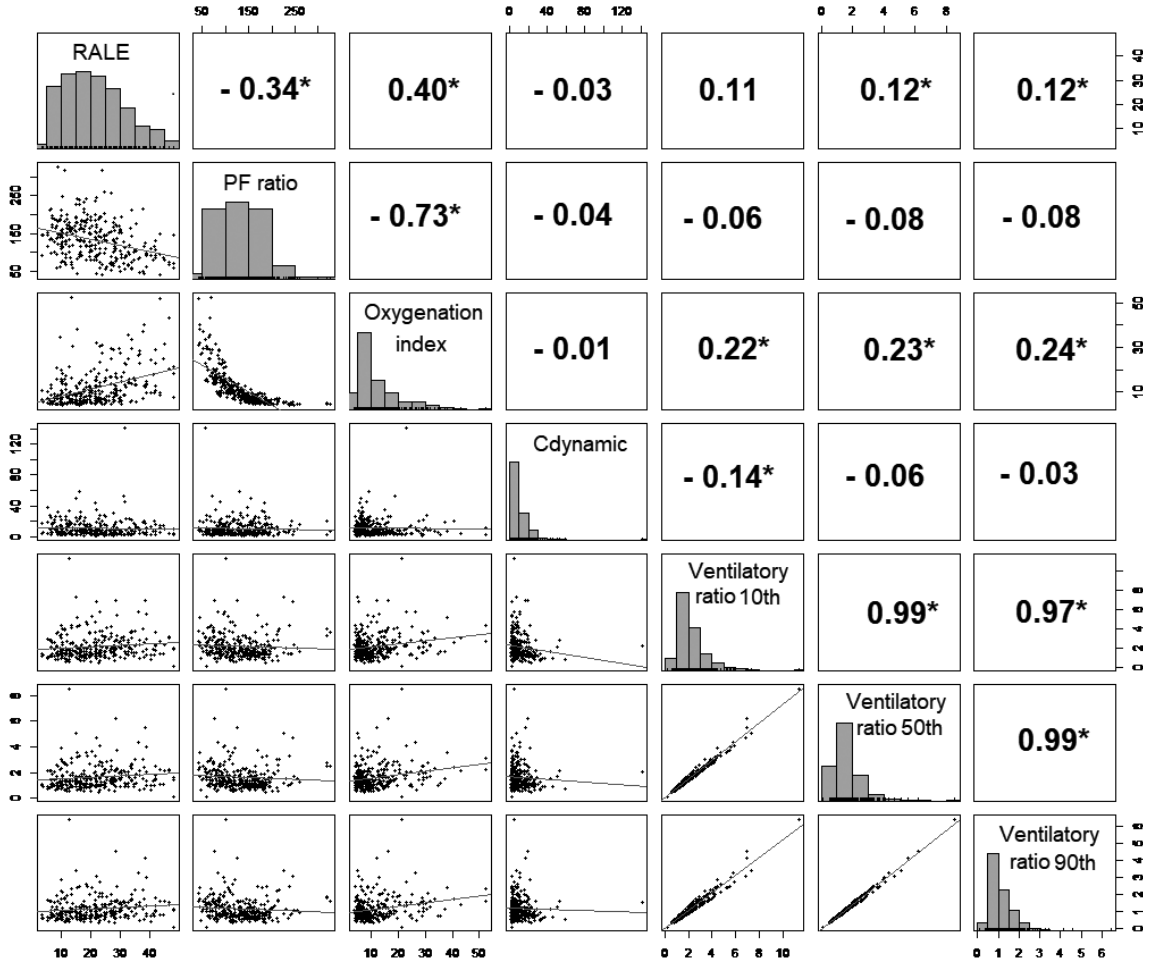

Fig. 2. Correlation between RALE scores and other acute respiratory distress syndrome severity index including PaO_2/FIO_2 (PF) ratio, oxygenation index, dynamic lung compliance, and ventilatory ratio 10th, 50th, and 90th. The correlation matrix showed the bivariate scatter plots on the bottom of the diagonal, the distribution of each variable as a bar chart on the diagonal, and the value of the Pearson coefficient on the top of the diagonal with asterisk marks for $p<0.05$. RALE, radiologic assessment of lung edema.

https://doi.org/10.3349/ymj.2022.0653

group, which were classified using a cut-off of 22 as decided by the Contal and O'Quigley method, there was a significant difference in the overall mortality (p=0.031). The difference in ARDS-specific mortality between the high and low RALE scores (cut-off of 18) was rather apparent, as shown in the survival curves, and statistically significant (p=0.003).

Table 2. Mortality Across Quartiles of the ARDS Severity Index

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* value
RALE score					
Overall mortality	26.1	20.5	33.8	38.7	0.030
ARDS-specific mortality*	18.3	16.9	29.4	39.1	0.002
PaO_2/FIO_2 ratio					
Overall mortality	49.3	30.1	23.7	16.2	<0.001
ARDS-specific mortality*	47.1	28.1	16.2	13.2	<0.001
Oxygenation index					
Overall mortality	14.9	19.7	31.0	53.3	<0.001
ARDS-specific mortality*	7.5	18.3	28.6	50.7	<0.001
Cdynamic					
Overall mortality	25.3	19.2	42.0	32.9	0.060
ARDS-specific mortality*	27.8	13.4	42.9	21.2	0.724
Ventilatory ratio 10th					
Overall mortality	29.7	25.7	28.0	36.5	0.344
ARDS-specific mortality*	17.6	17.6	22.7	37.8	0.003
Ventilatory ratio 50th					
Overall mortality	26.1	24.4	32.4	37.0	0.086
ARDS-specific mortality*	17.2	20.3	25.8	40.6	0.002
Ventilatory ratio 90th					
Overall mortality	24.3	29.3	27.0	39.2	0.076
ARDS-specific mortality*	14.9	18.7	23.0	39.2	<0.001

ARDS, acute respiratory distress syndrome; RALE, radiographic assessment of lung edema; Cdynamic, dynamic lung compliance.
Data are presented as %.
*ARDS specific mortality is the case of death from severe pulmonary dysfunction or requiring extracorporeal membrane oxygenation therapy.

For multivariable Cox regression analysis of ARDS-specific mortality, the variables we first accounted for are listed in Supplementary Table 4 (only online). The variables that showed a significant difference between the high and low RALE score groups (i.e., PALICC grade, PF ratio, OI, and VR 50th) were excluded for their risk of collinearity. Both mortality prediction models PIM-3, PRISM-3, already validated for direct correlation to mortality, were also excluded. The results of univariable analysis of all included variables and the results of multivariable analysis of variables that were significant in the univariable analysis are shown in Table 3. In the univariable analysis, the RALE score had an HR of 1.19 (95% CI, 1.18–3.11), which was statistically significant. Other significant variables included age, ARDS etiology, and comorbidity. In the multivariable analysis adjusted for the other significant variables, the RALE score had a significant HR of 1.77 (95% CI, 1.05–2.91). Hematologic or oncologic disease as a comorbidity was the only other variable that significantly contributed to ARDS-specific mortality with an HR of 4.15 (95% CI, 1.23–14.0).

Comparison of ARDS severity index as a predictor of PICU mortality

The results of the validation of ARDS severity indices, PIM-3, and PRISM-3 as predictors of mortality and ARDS-specific mortality are provided in Supplementary Table 5 (only online). For overall mortality, the RALE had a C-index of 0.575 (95% CI, 0.499–0.651), indicating no significance as a predictive index.[23] Composite mortality scores showed the highest C-index as expected: PIM-3, 0.693 (95% CI, 0.628–0.758) and PRISM-3, 0.749 (95% CI, 0.696–0.802). Among other ARDS indices, OI was the strongest predictor of overall mortality with a C-index of 0.637 (95% CI, 0.568–0.706), but it was not significantly different from the RALE score. The RALE score was a more significant predictor of ARDS-specific mortality than of overall mortality, with a C-index of 0.607 (95% CI 0.519–0.695);[23] this result was not significantly different from the C-indices of PIM-3 0.648 (95% CI,

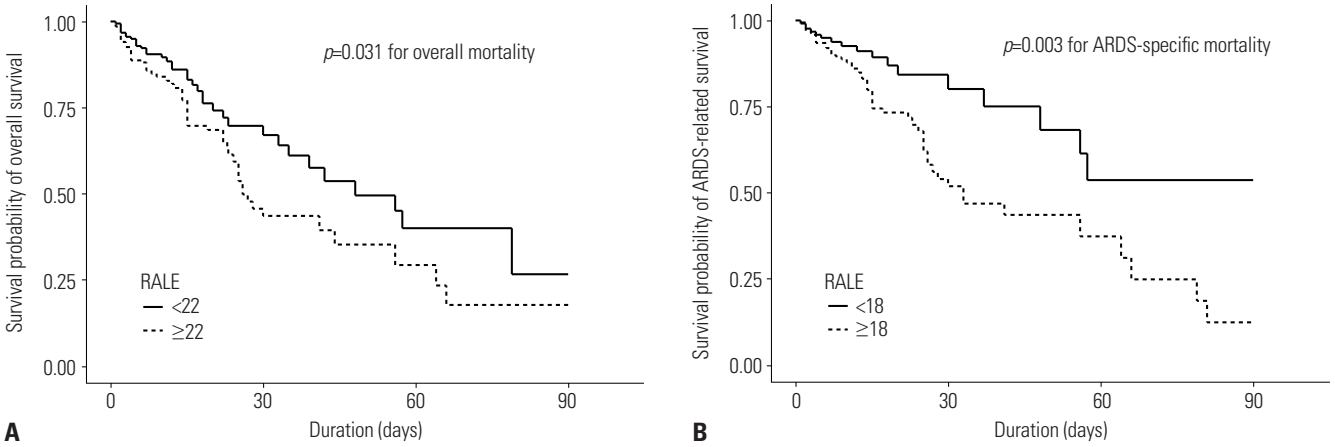

Fig. 3. Survival curves according to the RALE score. For overall mortality, the sample was divided into high RALE score group and low RALE score group using a cut-off of 22, with p=0.031 in the log-rank test (A). For ARDS-specific mortality, the sample was divided using a cut-off of 18, with p=0.003 in the log-rank test (B). ARDS, acute respiratory distress syndrome; RALE, radiographic assessment of lung edema.

Table 3. Univariable and Multivariable Cox Regression Analysis of ARDS-Specific Mortality* in Children

	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Age	1.060	1.02–1.10	0.005	1.020	0.97–1.07	0.535
Sex†	1.380	0.84–2.26	0.206			
ARDS etiology			<0.001			0.184
Infectious pneumonia	1.000			1.000		
Aspiration pneumonia	0.612	0.19–2.00	0.415	0.710	0.21–2.35	0.573
Sepsis	2.630	1.57–4.39	<0.001	1.810	1.00–3.28	0.050
Post CPR status	1.590	0.62–4.11	0.337	1.290	0.48–3.45	0.619
Comorbidity			<0.001			0.006
None	1.000			1.000		
Lung or airway diseases	1.570	0.47–5.30	0.464	1.870	0.54–6.39	0.321
Neurologic disease	0.700	0.19–2.63	0.596	0.730	0.18–2.87	0.649
Hematologic or oncologic disease	5.290	1.62–17.2	0.006	4.150	1.23–14.0	0.022
Genetic disorder or immune deficiency	1.340	0.27–6.68	0.719	1.670	0.33–8.48	0.539
Cdynamic	1.000	0.98–1.03	0.759			
RALE score	1.190	1.18–3.11	0.008	1.770	1.08–2.91	0.024

ARDS, acute respiratory distress syndrome; CI, confidence interval; CPR, cardiopulmonary resuscitation; Cdynamic, dynamic lung compliance; RALE, radiographic assessment of lung edema.
*ARDS specific mortality is the case of death from severe pulmonary dysfunction or requiring extracorporeal membrane oxygenation therapy; †Male sex as a reference.

0.554–0.742) and PRISM-3 0.697 (95% CI, 0.634–0.760), implying that the RALE score is not inferior to these composite mortality indices when predicting the ARDS-specific mortality. OI was the strongest predictor of ARDS-specific mortality among ARDS severity indices, with a C-index of 0.672 (0.597–0.748), not significantly different from that of the RALE score.

We compared the C-index of the RALE score and OI according to the PALICC grade. The performance of the RALE score and OI assessed by C-index was not significantly different according to the PALICC grade shown in Supplementary Table 6 (only online). We generated the combined index of the RALE score and OI from a multivariable cox regression model of these two variables as independent variables. The C-index of the combined index did not show any difference with that of the RALE score (Supplementary Table 5, only online). Since the ARDS-specific mortality showed significant differences in children having infectious pneumonia and sepsis as an ARDS etiology, we calculated the C-index in the subgroups who had infectious pneumonia and sepsis. The C-index of children having infectious pneumonia and sepsis were 0.641 (0.518–0.764) and 0.627 (0.478–0.776), respectively.

Restricted cubic-spline curves of mortality and ARDS-specific mortality for each ARDS severity index are shown in Fig. 4. Except for dynamic compliance for both overall mortality and ARDS-specific mortality, and VR for overall mortality, which were rather irrelevant, other ARDS severity indices showed noticeable correlation to the outcomes. It is noticeable that in the high ARDS severity score range, the overall mortality and ARDS-specific curve of the RALE score changed more sharply than those of OI, reflecting the better performance for prediction, while the curves of OI changed more sharply than those of RALE score in the low ARDS severity range. The better performance of RALE in the high ARDS severity score range indicates its usefulness in the prediction of prognosis of severe ARDS.

DISCUSSION

Herein, we evaluated the reliability of the RALE score and its feasibility as a prognostic marker of overall mortality and ARDS-specific mortality in children with ARDS. The RALE score was a reliable score with small inter-reviewer variance, and it was significantly correlated with other ARDS severity indices, including OI and PF ratio. In the survival analysis, its capacity for predicting mortality was significant, which was maintained even when adjusting confounders of age, etiology, and comorbidity. When evaluated with the C-index, a commonly used metric in survival analysis to evaluate how good a prediction model is, while feasibility of the RALE score as a predictive index for overall mortality was limited as evidence by an insignificant C-index, the RALE score was a useful marker for predicting ARDS-specific mortality, comparable to OI and mortality composite scores, including the PIM-3 and PRISM-3.[23]

The impact of the RALE score on clinical outcomes signifies the importance of pulmonary edema in clinical presentation and progress of pediatric ARDS.[24] Previous studies have shown that the fluid balance influences pulmonary edema in ARDS patients.[25] Among restrictive fluid therapy, promoting oxygenation and ventilation, and liberal fluid therapy for sufficient nutrition, finding the right balance is essential for proper man-

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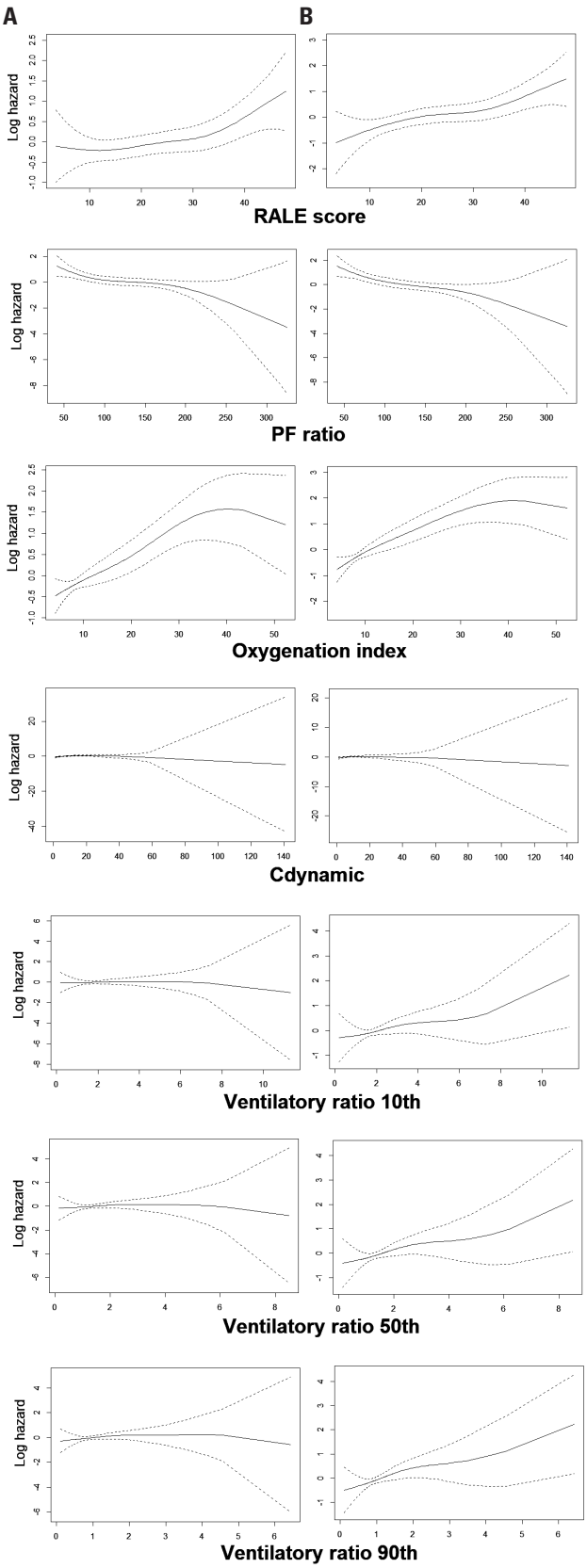

Fig. 4. Plots of acute respiratory distress syndrome (ARDS) severity index, including radiologic assessment of lung edema (RALE) score, PaO_2/FIO_2 (PF) ratio, oxygenation index, dynamic lung compliance, and ventilatory ratio 10th, 50th, and 90th against the outcomes, illustrating potential nonlinear relationships. A restricted cubic-spline model with three knots was fit for each measure, and log hazard ratio and 95% confidence interval estimates were plotted across the range of values for each measure for overall mortality (A) and ARDS-specific mortality (B).

agement of ARDS.[24-26] The RALE score provides the means to objectively evaluate and quantify pulmonary edema from chest radiographs, and this, in turn, helps clinicians determine whether a patient requires aggressive therapy for restrictive fluid balance, such as active use of diuretics or early application of continuous renal replacement therapy.[25]

We have proven that the RALE score is useful for the prediction of mortality outcomes, especially ARDS-specific mortality, where the RALE score was not inferior even to PIM-3 and PRISM-3.[17] Among ARDS severity indices, OI, which is currently incorporated in the PALICC definition of ARDS, was the most reliable.[1] However, the RALE score had aspects superior to OI, in terms of consistency of the restricted cubic-spline curves, with a greater proportional association with mortality in the high RALE score range. Although the combined index of the RALE score and OI could not show the better performance, these two indices could be complementary for evaluating the condition of children with ARDS, since OI is a tool for assessing oxygenation and the RALE score is a tool for determining pulmonary edema.[1,10] In a previous study on the RALE score of pediatric ARDS patients, the RALE score on day 3 since intubation was more strongly related to overall mortality compared to the RALE score on day 1.[11] This result is understandable since, given the rapid clinical deterioration of patients with severe ARDS, each day equates to significant progression to potential mortality.

In this study, among 88 non-survivors, 28 patients died from causes other than ARDS, such as sepsis or failure of the renal system. In most cases of mortality, the respiratory system was the main contributor to the outcome, in contrast to the results of previous studies on adult ARDS, where it was a minor cause.[4,27] While this difference may reflect that children are more vulnerable to failure of respiratory system, it is still important to note that not all deaths were directly caused by ARDS. Table 1 shows how sepsis as ARDS etiology, and hematologic or oncologic disease as comorbidity, were significantly related to mortality outcomes adds to the fact that different factors contribute to the death of ARDS patients. Most ARDS severity indices we evaluated showed better performance when predicting the ARDS-specific mortality than when predicting the overall mortality. In addition, we included 10 survivors who required ECMO therapy in the ARDS non-survivor group in order to reach a high prognostic value. From a clinical standpoint, differentiating patients with a higher risk of mortality or requiring ECMO treatment from patients with the a lower probability of either can be beneficial in deciding who should be treated more aggressively early on.[28]

Another notable difference between this study and previous studies on adult ARDS is that the RALE score significantly correlated with other ARDS severity indices, whereas the correlation between RALE scores and other indices were insignificant in adults.[4] In fact, in a previous study on children with respiratory failure, severity stratification based on chest radiography revealed a meaningful correlation to PF ratio.[29] Aggravation of pulmonary edema from fluid overload impacted the oxygenation status of pediatric patients with ARDS.[30] This difference may be due to the smaller lung reservoir of children, leading to quicker aggravation of ARDS, in turn causing oxygenation to be more sensitive to pulmonary edema.[25]

The previous study[11] on ARDS of children reported a rather surprising ICC of 98%, indicative of "excellent" reliability (above 90%). Our analysis revealed an ICC of 80.9%, which may be lower, but still considered to be "good" (between 75% and 90%).[22] The ICCs calculated for two separate pairs of reviewers from two separate centers both showed that the RALE score was reliable. While it is easy to suspect the RALE score to be influenced by subjective judgment of individual clinicians, we have shown that it is an objective and dependable measure to gauge disease severity based on chest radiography. In future studies, it may be useful to develop an artificial intelligence model with machine learning process to automatically calculate the RALE score from chest radiography data to guide clinical decisions in ICU.[31,32]

This study had several limitations. First, our data did not include patients admitted to neurosurgical and cardiac ICUs, and the exclusion of these patient groups may have led to biased results. However, considering that the cardiac cause of respiratory distress is excluded from the definition of ARDS, most of these patients would have been excluded from the patient selection process.[1] Second, this study was retrospective in nature, and the timepoint at which chest radiography data or blood gas study results were collected was not fixed among the patients. Rather, unlike previous studies which used definite events, such as intubation, as a starting point,[4,11] we searched for the time of disease onset for each patient, as per the PALICC definition of ARDS.[1] Considering the difference in the time of intubation among clinicians,[33] our study design may be suited for evaluating the disease severity at onset. Third, we only evaluated ARDS severity indices of disease onset, without further consideration of serial changes along disease progression. Further studies evaluating the performance of the RALE score as a measure for the progress of ARDS, including disease deterioration and therapy, are needed.

Despite the aforementioned limitations, this study had several strengths. We evaluated ARDS-specific outcomes, rather than limiting the analysis to overall mortality. The RALE cut-off scores were calculated using the Contal and O'Quigley method, making them suitable for survival analysis. Moreover, the performance of each ARDS severity index for survival analysis was objectively quantified and compared using the C-index, while the general pattern of correlation was observed using the restricted cubic-spline curve.

In conclusion, the RALE score is a reliable tool for stratifying ARDS severity in children and a useful prognostic marker for the prediction of mortality. The RALE score has shown good performance when predicting ARDS-specific mortality and effectively reflected the pulmonary edema status of the pa-

https://doi.org/10.3349/ymj.2022.0653

tients. They can provide useful information to clinicians when deciding on early application of aggressive therapy, such as ECMO, and serve as a guide to appropriately manage the fluid balance of children with ARDS.

ACKNOWLEDGEMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (grant number NRF-2021R1C1C1011294).

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https://doi.org/10.3349/ymj.2022.0653