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Original Article

Prognostic significance of serum apelin-13 and galectin-3 concentrations as potential indicators of severity and mortality in pediatric acute respiratory distress syndrome

Serçin Taşar[1], Nuri Alacakır[2], İsmail Bulut[1], Ayşe Esra Tapcı[1], Gül Kırtıl[3], Naz Koçoğlu[3], Rukiye Ünsal Saç[1], Medine Ayşin Taşar[4]

[1]Department of Pediatrics, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Türkiye; [2]Department of Pediatric Intensive Care, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Türkiye; [3]Department of Medical Biochemistry, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Türkiye; [4]Department of Pediatric Emergency, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Türkiye.

ABSTRACT

Background. The predictive and prognostic significance of apelin and galectin-3 as biomarkers in pediatric acute respiratory distress syndrome (PARDS) and lung injury has remained limited. This study examined the association between serum apelin-13 and galectin-3 levels, PARDS severity, and patient outcomes.

Methods. The study included children aged 1 month to 18 years diagnosed with PARDS on admission to a pediatric intensive care unit, alongside age- and sex-matched outpatient controls. PARDS was diagnosed and classified by severity according to Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) guidelines, based on oxygenation indices for non-invasive and invasive ventilation. Exclusion criteria included prior transplants, chronic lung disease, cyanotic congenital heart disease, prolonged ventilation, and other major conditions. After informed parental consent, 3 mL of peripheral venous blood was collected from all participants. Serum samples for apelin-13 and galectin-3 were stored at −80°C and analyzed using commercial enzyme-linked immunosorbent assay (ELISA) kits. Demographic, clinical, and laboratory data were systematically recorded for analysis.

Results. The study and control groups were comparable in age and gender. Patients had significantly lower hemoglobin, hematocrit, red blood cell, calcium, and phosphorus levels, and higher neutrophil counts, C-reactive protein, and liver enzymes. Apelin-13 levels did not differ significantly between groups, wheras median galectin-3 levels were significantly higher in patients (p=0.003). Apelin-13 levels were significantly lower and galectin-3 levels significantly higher with increasing PARDS severity. Severe PARDS was associated with lower PaO2/FiO2 ratios, arterial pH, and higher ventilator pressures. Mortality was 36.4% in severe and 22.7% in moderate PARDS. Serum galectin-3 level was the sole independent predictor of mortality (OR: 1.20, 95% CI 1.02–1.39, p=0.02).

Conclusion. Although the apelin/APJ system's role in acute lung injury is known, its diagnostic and prognostic value in PARDS requires further study. Galectin-3 levels correlate with disease severity and outcomes, highlighting the need for larger, age- and phenotype-homogenized studies to confirm its role as an independent mortality predictor.

Key words: apelin-13, biomarkers, galectin-3, pediatric acute respiratory distress syndrome (PARDS), prognosis.

✉ Serçin Taşar ▪ sercin_gozkaya@yahoo.com

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Pediatric acute respiratory distress syndrome (PARDS) remains a major cause of mortality and long-term morbidity in all age groups, from infants to adolescents, despite recent trends in the development of new diagnosis algorithms and attempts to standardize management over the past decade.[1] The incidence of PARDS was 3.2% in pediatric intensive care unit patients and 6.1% in pediatric patients on mechanical ventilation.[2] In 2015, the Pediatric Acute Lung Injury Consensus Conference (PALICC) introduced diagnostic criteria for PARDS that differed from those used for adults.[3] Despite research that has significantly advanced our understanding of the pathophysiology of PARDS, lung protection, and oxygenation[4,5], the latest update (Second International Guidelines for the Diagnosis and Management of PARDS [PALICC-2]) pointed out that supportive therapies, in addition to the diagnosis and definitive treatment of PARDS, are still not sufficiently standardized globally, particularly in settings with limited resources.[1,6]

PARDS is a heterogeneous clinical syndrome, and the lack of adherence to recommended principles in its diagnosis and management across individual pediatric intensive care units (PICUs) remains problematic.[7,8] Investigating the prognostic and predictive value of biomarkers that may help determine disease severity and outcomes could enhance the identification and management of patients with PARDS.[1] Apelin serves as an endogenous ligand for the G protein-coupled receptor APJ. The apelin/APJ system is proposed to mitigate pulmonary arterial hypertension within the respiratory system and possesses an intrinsic anti-injury mechanism against acute lung injury and acute respiratory distress.[9] Galectin-3, a ß-galactoside-binding lectin, is predominantly expressed by endothelial and alveolar macrophages and has been demonstrated to activate the host's inflammatory response through the induction of cytokine release.[10] Recent studies suggest that it plays a role in regulating the inflammatory and pulmonary responses, especially in PARDS that develops after coronavirus disease (COVID-19).[11,12] The predictive and prognostic significance of apelin-13 and galectin-3 as biomarkers in PARDS and lung injury has remained limited. This study examined the association between serum apelin-13 and galectin-3 levels, PARDS severity, and patient outcomes.

Methods

This observational cohort study obtained approval from the Ankara Training and Research Hospital Ethics Committee and was performed in accordance with the Declaration of Helsinki. The research was conducted between December 2023 and May 2025 in a pediatric intensive care unit at a tertiary care hospital. The study group was made up of children aged 1 month to 18 years diagnosed with ARDS upon their admission to the PICU. The control group was selected from children who had no chronic diseases, were not receiving medication, had no underlying lung disease and had no recent infection or lung disease. The control group comprised age and sex-matched volunteers who underwent blood tests in the pediatric outpatient department for various reasons, including young children seeking approval for kindergarten, adolescents undergoing routine blood checks prior to internships, and healthy children aged 9-12 months receiving routine hemogram and ferritin assessments. PARDS was diagnosed according to PALICC-2.[1] In children receiving non-invasive ventilation (facemask interface with continuous airway positive pressure/positive end-expiratory pressure ≥ 5 cm H2O), a PaO_2/FiO_2 ratio ≤ 300 or SpO_2/FiO_2 ratio ≤ 250 indicated PARDS. For those on invasive mechanical ventilation, an oxygenation index (OI = mean airway pressure x FiO_2/PaO_2) ≥ 4 was used to define PARDS. Four hours following diagnosis, the severity of PARDS was categorized as follows: mild PARDS was defined as 4≤OI<8, moderate as 8≤OI<16, and severe as ≥16. Exclusion criteria included having a solid organ transplant, hematopoietic stem cell transplant, lung cancer, a positive human immunodeficiency virus (HIV) test,

a history of respiratory failure or pulmonary edema from heart failure, exacerbation of chronic lung disease, being ventilator dependent, having cyanotic congenital heart disease, or being on ventilators for more than seven days prior to $PaO_2/FiO_2 \leq 300$. Parental consent was obtained after informing them that the laboratory samples collected from the children would be utilized and presented anonymously for scientific purposes, and that the research involved no invasive procedures.

The demographic data, baseline complete blood count (CBC), and laboratory parameters of both patients and controls were collected, while patients' vital parameters, mechanical ventilation values, and arterial blood gas variables were recorded during the intensive care period. The Pediatric Risk of Mortality (PRISM III) score, a widely used severity-of-illness scoring system in PICUs, was included to assess the risk of mortality and to adjust for disease severity in the analysis. We obtained 3 mL of peripheral venous blood from patients at the first hour and controls for baseline laboratory tests and serum samples that were separated from the same sample for apelin-13 and galectin-3 levels were stored at −80 °C. The samples were then prepared according to the manufacturer's recommendations using commercial enzyme-linked immunosorbent assay (ELISA) kits. The normal ranges for apelin-13 and galectin-3 were 1.4-94.8 ng/mL and 19.75-1600, respectively.

Statistical analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software version 19.0. The normal distribution of variables was assessed through visual methods, including histograms and probability plots, as well as analytical methods (Kolmogorov-Smirnov test and the Shapiro-Wilk test). Laboratory and clinical parameters that followed a normal distribution were presented as mean ± standard deviation, whereas those that did not conform to normality were reported as median and interquartile ranges. Given the further reduction in sample size after age stratification, serum apelin-13 and galectin-3 levels were summarized using medians and interquartile ranges Categorical variables were represented as numerical values and percentages. The chi-square test was used to compare categorical variables between the control and study groups. Independent samples t-test or Mann-Whitney test was used to compare continuous variables, depending on normal distribution. For the comparison of variables among three PARDS severity classes, One-way ANOVA was employed for normally distributed continuous variables, whereas the Kruskal-Wallis test was utilized for non-normally distributed variables. Spearman's correlation was used to assess the association between apelin-13 and galectin-3 levels and baseline characteristics, as well as clinical and ventilatory parameters of PARDS. A univariate logistic regression analysis was conducted to assess the relationship between study parameters and mortality. In the context of multivariate analysis, variables identified in univariate analysis were subsequently included in logistic regression analysis to ascertain the independent predictors of mortality. Variables were selected for multivariate logistic regression based on clinical relevance and univariate analysis results. Parameters with $p<0.10$ in univariate analysis were considered candidates and were entered into the multivariate model using the enter method (forced entry), rather than an automated stepwise approach. Model performance was evaluated by the Omnibus test of model coefficients for overall goodness-of-fit and by the Nagelkerke R^2 to assess the explanatory power of the multivariate logistic regression model. The Omnibus test demonstrated a statistically significant overall model fit ($\chi^2 = 31.49$, $p<0.001$). The model showed good explanatory power with a Nagelkerke R^2 of 0.80. Discrimination was acceptable, and model convergence was achieved without instability. A receiver operating curve (ROC) analysis was performed to evaluate the diagnostic performance of galectin-3 for pediatric acute respiratory distress syndrome (PARDS). A p value of 0.05 was used for statistical significance.

Power analysis

A post-hoc power analysis was performed using G*Power (version 3.1.9.4) to assess the difference in galectin-3 levels between PARDS patients and controls. The analysis yielded an effect size of 0.86, corresponding to a statistical power of 98.9% (1-β error probability) at a two-tailed $\alpha = 0.05$.

Results

Among the 44 patients, the etiology of PARDS was bronchopneumonia in 20 (45.5%), viral pneumonia in 17 (38.6%), sepsis in 5 (11.4%), and ventilator-associated pneumonia in 2 (4.6%). The age and gender distributions were comparable between groups (Table I). Mean values for hemoglobin (p<0.001), hematocrit (p<0.001), red blood cells (p<0.001), calcium (p<0.001), and phosphorus (p=0.003) were significantly lower and absolute neutrophil count (p<0.001), C-reactive protein (p<0.001), and liver function enzymes (p=0.005) were significantly higher in patients than in controls. The median serum apelin-13 level did not differ significantly between the study group and controls (p=0.32) but the median galectin-3 level was significantly elevated in the study group (p=0.003). Although there were marked differences in both serum apelin-13 and galectin-3 levels across different age subgroups, these differences were not statistically significant (Table II).

Table I. Comparison of demographics and baseline laboratory parameters between study patients and controls

Variable	Study group (n=44)	Control group (n=44)	p
Age (months)	42 (2-204)	48 (2-204)	0.68
Female gender, n (%)	18 (40.9)	18 (40.9)	0.99
Laboratory parameters			
Hemoglobin (g/dL)	9.8±1.5	12.2±1.5	**<0.001**
Hematocrit (%)	29.7±4.4	36.7±4.3	**<0.001**
RBC ($\times 10^6$ /μL)	3.6 (2.4-6.7)	4.7 (3.4-5.4)	**<0.001**
WBC ($\times 10^3$ /μL)	11.7 (8.4-16.4)	8.7 (4.6- 19.3)	0.01
Platelets ($\times 10^3$ /μL)	299 (18-902)	322 (146-802)	0.12
ANC ($\times 10^3$ /μL)	5.9 (1.1-25.8)	3.4 (0.8-13.3)	**<0.001**
ALC ($\times 10^3$ /μL)	2.5 (0.5-12.8)	3.8 (0.8-12.5)	0.02
CRP (mg/dL)	32.6 (0.9-345.7)	0.7 (0.1-16.8)	**<0.001**
ALT (U/L)	26.5 (6-245)	14.5 (7-41)	**0.005**
AST (U/L)	40.5 (18-527)	32 (16-58)	**0.005**
Urea (mg/dL)	20 (2-86)	22.5 (6-36)	0.37
Creatinine (mg/dL)	0.22 (0.6-2.8)	0.33 (0.21-0.79)	0.05
Sodium (mmol/L)	138.5 (124-161)	138 (131-144)	0.3
Potassium (mmol/L)	4.36±0.64	4.62±0.38	0.07
Chloride (mmol/L)	105 (92-130)	104 (99-111)	0.27
Calcium (mg/dL)	8.73±1.06	10.01±0.47	**<0.001**
Phosphorus (mg/dL)	3.9 (0.89-9.96)	4.7 (3.1-6.4)	**0.003**
Serum apelin-13 level (pg/mL)	649.6 (172.8-4000)	753.9 (223.4-4000)	0.32
Serum galectin-3 level (ng/mL)	6.65 (0.44-58.03)	2.53 (0.58-13.48)	0.003

Data presented as number (percentage), mean±SD, or median (interquartile range). ALC: absolute lymphocyte count, ALT: Alanine aminotransferase, ANC: absolute neutrophile count, AST: Aspartate aminotransferase, CRP: C-reactive protein, RBC: Red blood cell, SD: standard deviation, WBC: White blood cell.

Table II. Comparison of serum apelin-13 and galectin-3 levels across age-stratified groups

Variable	Serum apelin-13 level (pg/mL)			Serum galectin-3 level (ng/mL)		
	Study group	Control group	p	Study group	Control group	p
0 to 1 years (n=17)	487.43 (338.42-1936.00)	695.58 (358.74-951.10)	0.96	6.32 (1.84-24.87)	4.20 (1.43-7.53)	0.36
1 to 5 years (n=35)	1282.88 (522.09-2906.67)	911.67 (741.33-1712.00)	0.90	8.63 (1.43-21.83)	2.27 (1.36-2.82)	0.09
5 to 12 years (n=16)	497.97 (437.50-719.20)	651.42 (451.73-837.54)	0.57	8.56 (2.24-18.22)	2.52 (1.56-4.79)	0.10
12 to 18 years (n=20)	619.09 (423.78-911.67)	617.51 (575.71-3013.33)	0.57	5.19 (1.77-21.20)	5.03 (1.21-8.09)	0.39

Data presented as median (interquartile range).

Table III. Comparison of hemodynamic and respiratory parameters among three PARDS categories in study patients

Variable	Mild PARDS (n=11)	Moderate PARDS (n=22)	Severe PARDS (n=11)	p
OI	6.33±0.80	10.92±1.99	51.35±67.92	**<0.001**
Oxygen saturation (%)	99 (98-99)	98 (96-99)	96 (91-98)	0.04
Heart rate (/min)	125.54±22.88	119.72±23.68	134.36±22.47	0.24
Systolic BP (mmHg)	96.00±12.07	100.86±14.26	92.81±8.68	0.2
Diastolic BP (mmHg)	57.54±9.32	60.36±12.56	53.81±7.16	0.26
Respiratory parameters				
PEEP (cm H_2O)	5.27±0.47	5.32±0.78	7.45±2.77	**0.007**
PS above PEEP (cm H_2O)	14.00±4.05	18.55±8.34	23.09±8.06	**0.01**
FiO_2 (%)	60.00±0.00	60.00±0.00	60.00±0.00	1
MAP (cm H_2O)	10.36±3.59	13.02±3.40	17.36±4.13	**0.001**
Peak pressure (cm H_2O)	19.09±4.06	23.18±8.81	30.27±10.74	**0.01**
VTE (mL/kg)	136.91±86.25	126.14±79.14	150.27±111.67	0.83
Frequency (/min)	25.55±104.25	27.41±10.81	30.64±8.03	0.22
APRV (cm H_2O)	0 (0)	1 (4.5)	2 (18.2)	0.2
MV duration (days)	5.27±0.47	5.32±0.78	7.45±2.77	0.25
Arterial blood gas				
pH	7.37±0.06	7.37±0.11	7.24±0.16	**0.01**
pCO_2 (mm Hg)	49.5 (40.2-57.2)	50.2 (29-81)	49.9 (28.3-87.4)	0.92
HCO_3 (mmol/L)	28.36±4.27	28.14±5.10	23.95±6.56	0.08
BE (mmol/L)	3.14±5.00	2.73±5.38	-1.99±7.52	0.07
Lactate (mmol/L)	0.9 (0.3-25)	1.4 (0.3-6)	2.1 (0.5 – 13.9)	0.26
PaO_2/FiO_2	147.36±55.06	139.30±119.65	68.73±16.30	**0.001**
ICU stay (days)	3.64±1.36	8.36±18.50	7.18±5.19	0.3
Hospital stay (days)	5.55±1.75	11.14±19.48	13.18±9.02	0.06
Mortality (%)	0 (0)	5 (22.7)	4 (36.4)	0.1

Data presented as number (percentage) or median (interquartile range) Severity of PARDS was described based on OI: Oxygenation index value which was calculated based on MAP x FiO_2/PaO_2. Mild PARDS was defined as 4≤OI<8, moderate as 8≤OI<16 and severe as ≥16.

APRV: Airway pressure release ventilation, BP: Blood pressure, FiO_2: Fraction of inspired oxygen, MAP: Mean airway pressure, MV: Mechanical ventilation, OI: Oxygenation index, PARDS: Pediatric acute respiratory distress syndrome PaO_2: Partial arterial oxygen pressure, PEEP: Positive end-expiratory pressure, PS: Pressure support, VTE: Exhaled tidal volume.

Female gender was significantly more common in patients with severe PARDS compared to those with mild or moderate PARDS, but there were no significant differences in CBC, kidney and liver functional tests, or electrolyte values across the three severity categories. The median serum apelin-13 levels (p=0.002) and median galectin-3 levels (p<0.001) exhibited significant differences among the three groups. In pairwise group comparisons, the difference in median apelin-13 levels between patients with mild and moderate PARDS was not significant (p=0.10). However, median apelin-13 values in patients with severe PARDS were significantly lower than those in both mild PARDS (p<0.001) and moderate PARDS (p=0.006). Median galectin-3 levels were significantly elevated in both moderate PARDS compared to mild PARDS (p=0.04) and in severe PARDS compared to moderate PARDS (p=0.006) (Supplementary Table S1).

The only notable differences in hemodynamic and respiratory parameters between the three PARDS categories were that severe PARDS patients had significantly lower PaO_2/FiO_2 ratios (p<0.001), arterial blood gas pH (p=0.01), OI (p<0.001) and mechanical ventilator pressure values (p=0.007 for positive end-expiratory pressure [PEEP], p=0.01 for pressure support [PS] above PEEP, and p<0.001 for mean airway pressure [MAP]). Patients with mild PARDS exhibited shorter durations of intensive care and hospital stays; however, these differences did not achieve statistical significance (p<0.06). All patients with mild PARDS survived to discharge, but four (36.4%) of those with severe PARDS and five (22.7%) of those with moderate PARDS died of sepsis and multiorgan failure (Table III, Table IV). Serum galectin-3 level (odds ratio [OR]: 1.23, 95% confidence interval [CI]: 1.05-1.44, p=0.01) and PRISM III score (OR: 1.29, 95% CI: 1.039-1.602, p=0.02) were identified as univariate predictors of mortality. In multivariate analysis, serum galectin-3 level emerged as the sole independent predictor of mortality (OR: 1.20, 95% CI: 1.02-1.39, p=0.02). PRISM III score was found to be statistically signicifant for galectin-3, and OI was found to be significant for both galectin-3 and apelin-13 (p<0.001) (Table V). The ROC analysis demonstrated that galectin-3 had a statistically significant discriminatory ability (AUC = 0.68, 95% CI: 0.56–0.79, p = 0.03) (Supplementary Fig. S1). The optimal cut-off values (3.0, 3.07,

Table IV. Spearman correlation coefficients of apelin-13 and galectin-3 levels with clinical and laboratory parameters

Variable	Apelin-13		Galectin-3	
	r	p	r	p
Age	-0.02	0.89	-0.008	0.95
PRISM III Score	-0.26	0.08	0.57	**<0.001**
OI	-0.532	**<0.001**	0.67	**<0.001**
PS above PEEP	-0.316	0.03	0.247	0.10
Peak pressure	-0.395	**0.008**	0.276	0.07
MAP	-0.31	**0.04**	0.322	**0.03**
MV duration	-0.159	0.30	0.178	0.24
PaO_2/FiO_2	0.451	**0.002**	-0.277	0.069
PCO_2	0.041	0.79	-0.102	0.51
ICU stay	-0.003	0.98	0.187	0.22
Hospital stay	-0.115	0.45	0.176	0.25

FiO_2: Fraction of inspired oxygen, ICU: Intensive care unit, MAP: Mean airway pressure, MV: Mechanical ventilation, OI: Oxygenation index, PaO_2: Partial arterial oxygen pressure, PEEP: Positive end-expiratory pressure, PRISM: Pediatric risk of mortality, PS: Pressure support.

Table V. Univariate and multivariate predictors of mortality

Variable	p	OR	95% CI
Univariate predictors			
Age	0.29	1.00	0.995-1.017
PRISM III Score	**0.02**	1.29	1.039-1.602
OI	0.66	1.00	0.987-1.021
PS above PEEP	0.14	1.06	0.978-1.165
Peak pressure	0.06	1.07	0.996-1.161
MAP	0.12	1.14	0.964-1.370
MV duration	0.09	1.14	0.976-1.352
PaO_2/FiO_2	0.25	0.99	0.974-1.007
pCO_2	0.11	0.94	0.870-1.015
Apelin-13 level	0.11	0.99	0.994-1.001
Galectin-3 level	**0.01**	1.232	1.050-1.446
Multivariate predictors			
Galectin-3 level	**0.02**	1.20	1.02-1.39
PRISM III score	0.25	1.09	0.94-1.26

CI: confidence interval, MAP: mean airway pressure, MV: mechanical ventilation, OI: oxygenation index, OR: odds ratio, PEEP: positive end-expiratory pressure, PRISM: pediatric risk of mortality, PS: pressure support.

Table VI. ROC curve analysis of galectin-3 cut-off values for the diagnosis of pediatric acute respiratory distress syndrome (PARDS)

Cut-Off	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)
3.0	65.9	59.1	61.7	63.4
3.07	65.9	61.4	63.0	64.3
3.37	61.4	63.6	62.8	62.2

NPV: Negative predictive value, PPV: Positive predictive value.

and 3.37 ng/mL) along with corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented in Table VI.

Discussion

Apelin-13 and particularly galectin-3 may serve as significant markers for the diagnosis, severity, and prognosis of PARDS. The study group had slightly higher median serum apelin-13 levels. However, mean galectin-3 levels were significantly higher—approximately threefold—than those in controls, with no notable changes observed in other laboratory parameters, including markers of multi-organ function, sepsis, or electrolyte values. Moreover, galectin-3 has the potential to function as a direct indicator of compromised respiratory function in PARDS, as it independently predicted mortality and exhibited a strong positive correlation with the PRISM III score, oxygenation index, and mean arterial pressure.

Many studies have investigated a wide range of biomarkers, including known inflammatory markers, such as C-reactive protein, granulocyte–macrophage colony-stimulating factor, human neutrophil elastase, and interleukins to predict the prognosis of PARDS in advance, and to guide treatment against clinical deterioration. It has been reported that coagulation and fibrinolysis parameters (e.g. antithrombin III and

plasminogen activator inhibitor-1), various epithelium-derived molecules (e.g. CC16/CC10, sICAM-1), endothelium-derived molecules (e.g. angiopoietin-2, endothelin-1, von Willebrand factor), surfactant proteins, and B-type natriuretic factor serve as significant markers in distinguishing non-survivors among children with PARDS.[13,14] However, efforts to revalidate biomarkers with prognostic value in adult ARDS for use in PARDS face challenges due to the fact that PARDS diagnostic criteria have only been standardized for about 10 years, and because the overall incidence of PARDS is low.[15]

The heterogeneity of PARDS arises not only from the complexity of the underlying pathology but also from factors such as age-related changes in lung capacity, the immune system, and other comorbid conditions in children. The general consensus in recent years has been to reduce the uncertainty caused by this heterogeneity in PARDS patients by identifying patient subgroups through biomarker-based enriched prognostic and predictive approaches. This strategy aims to support a targeted, individualized approach in both medical treatment and mechanical ventilation management to reduce mortality.[8] In fact, as in adults, it was recently demonstrated through latent class analysis that PARDS also has two phenotypes: hypoinflammatory and hyperinflammatory. This study highlighted the importance of phenotype-targeted therapy by reporting that phenotype-2 PARDS, characterized by markedly elevated levels of biomarkers such as angiopoietin-2, interleukin-1 receptor antagonist, interleukin-6, and interleukin-8, is associated with longer intensive care stays, prolonged mechanical ventilation, and higher mortality.[16]

The demonstration that the apelin/APJ system provides pleiotropic protection against acute lung injury and PARDS — by reducing mitochondrial reactive oxygen species (ROS)-triggered oxidative damage, mitochondrial apoptosis, and the inflammatory response induced via nuclear factor kappa B (NF-κB) and NOD like receptor containing pyrin domain (NLRP)3 inflammasome activation, as well as by triggering various other signaling pathways — has increasingly positioned it as a potential therapeutic target.[9,17] However, to date, no other studies in children have been reported apart from a single study by Zhang et al, which found that cord plasma apelin levels were significantly higher in preterm infants with respiratory distress compared to those without respiratory distress (158.9 ± 24.8 vs. 125.2 ± 18.2 pg/mL, respectively).[18] In our study, although apelin-13 levels in the PARDS group were higher than in the control group, this difference was not statistically significant; interestingly, apelin-13 levels were inversely correlated with increasing disease severity. Indeed, certain isoforms of apelin, which are indicators of the apelin/APJ system playing an essential role in vascular endothelial cell homeostasis, have been found to be low rather than elevated in pulmonary hypertension.[19] Furthermore, it has been reported that apelin levels acutely decrease and remain low for weeks in patients with vulnerable coronary artery plaques and acute myocardial injury.[20,21] Nevertheless, the literature still lacks data providing normal ranges of apelin levels in children across different age groups, and there is no evidence yet to determine which range of apelin levels in PARDS could reliably predict prognosis.

Although we did not find a statistically significant difference in apelin-13 levels between the overall patient and control groups ($p = 0.32$), the clear inverse relationship between disease severity and apelin-13 concentrations ($p = 0.002$) suggests that apelin-13 may function more as a dynamic marker of pulmonary injury progression than as a static indicator of disease presence. In support of this, multiple mechanistic and preclinical studies highlight plausible pathways by which apelin signaling may become depleted or suppressed as lung injury advances. For example, Lian et al.[22] demonstrated that in a ventilator-induced lung injury (VILI) animal model, exogenous apelin-13 reduced inflammation, oxidative stress, and apoptosis in lung tissue,

indicating that activation of the apelin/APJ axis may be a compensatory, protective response that is overwhelmed in severe injury states. Further, apelin has been shown to attenuate lipopolysaccharide (LPS)-induced acute lung injury via modulation of the Sirtuin 1 (SIRT1)/NLRP3 signaling pathway—thus suppressing endothelial cell pyroptosis and maintaining barrier integrity.[23] In another study apelin-13 was demonstrated to alleviate LPS-induced acute lung injury by inhibiting ROS generation, NF-κB activation, and NLRP3 inflammasome signaling.[24] Additionally, a recent study by Chen et al. showed that apelin-13 can preserve alveolar epithelial barrier function in LPS-induced injury, reducing edema and inflammatory cytokine leakage.[25] Taken together, these findings suggest that declining apelin-13 levels with increasing disease severity may reflect exhaustion of a local protective or reparative apelin/APJ response, impairment of endothelial–epithelial cross-talk, or enhanced peptide degradation.

The evidence supporting the role of galectin-3 levels in predicting worse outcomes in adult ARDS can be considered strong. In one study, galectin-3 levels in adult ARDS patients were significantly higher in survivors than in non-survivors (median [interquartile range]: 12.37 [7.94–18.79] vs. 5.01 [4.15–5.69] ng/mL, respectively, $p < 0.0001$), and a cut-off level of 10.59 ng/mL showed a sensitivity of 81.48% (95% CI: 0.62–0.94), although the specificity was not very high (55.56%; 95% CI: 0.38–0.72).[26] Another study reported that in 156 adult patients with ARDS due to COVID-19, elevated galectin-3 levels were a strong predictor of 30-day mortality, with risk significantly increased at levels above 35.3 ng/mL.[11] However, the most promising and convincing study on the diagnostic and prognostic role of galectin-3 in PARDS was a recent prospective case control study in 12 children with sepsis by Yehya et al.[27] The researchers showed, through plasma co-immunoprecipitation and downstream proteomics within 24 hours of ICU admission, that among the top 50 differentially expressed DNA-bound proteins, galectin-3 binding protein was the most informative discriminating protein for distinguishing children with PARDS from those without, thereby opening the door to the clinical translation of these findings. In our study, galectin-3 levels in patients were on average about four times higher than in controls, and showed a steady increase with increasing disease severity. Nevertheless, although galectin-3 emerged as an independent predictor of mortality in our multivariate model, its receiver operating characteristic - area under the curve (ROC AUC) of 0.68 suggests only moderate discriminative ability. Therefore, this finding must be treated cautiously rather than presented as definitive. Galectin-3 is unlikely to replace established clinical or laboratory prognostic tools, but may have additive value when integrated into a multimarker panel or risk score.

The main limitations of this study were its single-center and non-randomized design. The low incidence of PARDS also resulted in the constraint of a small sample size. Although both apelin-13 and galectin-3 levels differed by several fold across different severity levels, it should be considered that the heterogeneous age distribution of the children in the study group may have influenced the results regarding the predictive roles of apelin-13 and galectin-3 levels. Moreover, given the scarcity of pediatric-specific investigations on apelin and galectin levels, the generalizability and interpretation of our findings remain limited and should be considered with caution.

In conclusion, although the role of the apelin/APJ system in vascular endothelial homeostasis during acute lung injury has been demonstrated, more convincing studies are warranted to establish its diagnostic and predictive role in PARDS. Galectin-3 levels show a strong correlation with disease severity and outcome parameters, and further research is justified in larger studies involving age- and phenotype-homogenized pediatric subgroups to confirm galectin-3 as an independent predictor of mortality in PARDS.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2026.6648.

Ethical approval

The study was approved by University of Health Scienses Ankara Training and Research Hospital Ethics Committee (date: 06.12.2023, number: E-23-1434).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: ST, NA, AET, MAT; data collection: NA, İB, AET, GK, NK; analysis and interpretation of results: ST, GK, NK, RUS, MAT; draft manuscript preparation: ST, MAT. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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