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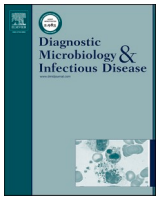

Original Article

The role of Copeptin in viral lower respiratory tract infections in child: A prospective case-control study

Berker Okay [a,*], Halil Ugur Hatipoglu [b], Zeynep Uze Okay [b], Cevher Kızılırmak [b], Ahsen Guler [b], Kâmil Sahin [b], Gulsen Akkoc [c]

[a] Istanbul Medipol University, Department of Pediatrics, Bahçelievler, Istanbul, Turkiye
[b] University of Health Sciences, Haseki Training and Research Hospital, Department of Pediatrics, Sultangazi, Istanbul, Turkey
[c] Marmara University, Pendik Training and Research Hospital, Department of Pediatric Infectious Diseases, Pendik, Istanbul, Turkey

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ABSTRACT

Background: Lower respiratory tract infection (LRTI) is a leading cause of morbidity and mortality among children globally. Copeptin, released by the pituitary gland, serves as a biomarker for various conditions and, as a neuroendocrine stress hormone, is useful in acute conditions. This study aimed to determine the role of copeptin levels in LRTI in children and whether it can reliably predict pneumonia severity.

Materials and Methods: This prospective case-control study was performed between April and October 2023. The study included four groups: (i) patients diagnosed with bronchiolitis (Group 1, n=25), (ii) patients diagnosed with mild to moderate pneumonia (Group 2, n=25), (iii) patients diagnosed with severe pneumonia (Group 3, n=25), and (iv) a control group (Group 4, n=26).

Results: Copeptin values differed significantly between the groups ($p<0.001$ for all comparisons). Copeptin demonstrated a sensitivity of 87.4 % and specificity of 82.2 % for distinguishing between patients with bronchiolitis and pneumonia, using a cut-off value of >0.586 ng/ml. For the identification of patients with severe pneumonia versus those with mild to moderate pneumonia, copeptin exhibited a sensitivity of 97.9 % and specificity of 94.7 % with a cut-off value of >1.215 ng/ml. The copeptin level exhibited a positive correlation with fibrinogen and FAR levels while demonstrating a negative correlation with albumin levels (r=0.354, $^{**}P$=0.002; r=0.408, $^{***}P<0.001$; and r=−0.334, $^{**}P$=0.003, respectively).

Conclusions: Copeptin demonstrates potential as a predictor of disease severity in children with pneumonia. It can also serve as a valuable tool to guide physicians in differentiating between bronchiolitis and pneumonia, as well as in diagnosing severe pneumonia.

1. Introduction

Copeptin, the precursor of arginine vasopressin (AVP), emanates from the pituitary gland and serves as a biomarker for various conditions [1]. It has established roles in the regulation of endothelial dysfunction, inflammation, and water-electrolyte balance [1]. The measurement of AVP levels poses challenges due to its brief half-life and the complexity of the requisite detection methods. In contrast, copeptin provides an indirect means of gauging circulating AVP levels, as it can be conveniently assessed through a sandwich immunoassay [1]. As a neuroendocrine stress hormone, copeptin functions as a prognostic indicator of an individual's stress burden. Moreover, its applicability extends to various acute conditions such as ischemic stroke or myocardial infarction [2]. Notably, copeptin is proven to be a dependable tool in the differential diagnosis of diverse ailments characterized by polyuria and polydipsia [2].

Lower respiratory tract infection (LRTI) is the predominant cause of morbidity and mortality among children and adolescents globally [3].

List of abbreviations: AUC, under the ROC curve; AVP, arginine vasopressin; CRP, C-reactive protein; ELISA, Enzyme-Linked Immunosorbent Assay; FAR, fibrinogen-to-albumin ratio; LRTI, Lower respiratory tract infection; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

* Corresponding author. Istanbul Medipol University, Department of Pediatrics, Bahçelievler/Istanbul, Turkiye, Çobançeşme, Fatih Cd. No:1/8 34196 Bahçelievler, İstanbul, Turkey.
E-mail address: drberkerokay@gmail.com (B. Okay).

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Copeptin has demonstrated notable utility in forecasting the severity and complications of severe pneumonia in adults [4,5]. However, while early investigations into copeptin's role in pediatric LRTI suggest its potential for diagnosing pneumonia and predicting complications, these studies present conflicting results [6–10].

Although there has been a notable increase in studies on copeptin in pediatric patients over the past decade, research specifically exploring its correlation with LRTI remains scarce. This prospective case-control study was designed to investigate the potential association between copeptin levels and the severity of illness in pediatric patients with LRTI. The study aimed to determine whether copeptin levels can serve as a reliable indicator of pneumonia severity and to differentiate between bronchiolitis and pneumonia, thereby providing valuable information for clinical practice. Furthermore, copeptin levels were compared with other acute phase reactants (C-reactive protein, neutrophil-to-lymphocyte ratio, fibrinogen-to-albumin ratio and procalcitonin) to ascertain which biomarkers are more efficacious in assessing pneumonia severity. The results of this study may significantly enhance our understanding of the role of copeptin in diagnosing LRTI, thus facilitating the development of more effective diagnostic and therapeutic approaches. Additionally, the study aimed to establish a cut-off value for copeptin in assessing pneumonia severity in pediatric patients diagnosed with pneumonia.

2. Materials and methods

2.1. Study setting and participant selection

The present study was structured as a prospective case-control investigation. Participants were recruited between April 12 and October 02, 2023, with patients sourced from the pool of hospitalized individuals and controls drawn from those attending pediatric outpatient clinics for routine checks or examinations at University of Medical Sciences Istanbul Haseki Training and Research Hospital. The study was conducted at a tertiary care academic hospital located in the inner city.

2.2. Diagnostic criteria

The study encompassed patients aged between 3 month and 5 years, without any chronic illnesses, and diagnosed with LRTI. The decision to restrict the study to children under 5 years of age was motivated by the aim of mitigating potential differences between the groups due to variations in the causative agents of pneumonia in school-age children. In children under 5 years of age, the most common cause of LRTI is viral infections [11]. Patients under 3 months of age were excluded from the study in accordance with the pneumonia severity guideline [12]. Exclusion criteria encompassed individuals with underlying lung conditions (such as cystic fibrosis, bronchopulmonary dysplasia, asthma, bronchiectasis, or tuberculosis) and chronic illnesses (including heart, kidney, liver, gastrointestinal, and endocrine disorders), those with a culture-proven diagnosis of bacterial LRTI, as well as patients who were receiving antibiotic treatment. Since confirming the diagnosis of bacterial infection required additional time, copeptin samples were collected from these patients at the time of admission, but they were excluded from the study once the bacterial infection was confirmed. Patients who had been hospitalized in the previous 72 hours, or who had conditions known to alter copeptin levels, such as obesity or malnutrition, laboratory-confirmed hyponatremia, or signs of dehydration, were also excluded. Informed consent was procured from the parents of each child eligible for inclusion in the study. Those patients whose parents did not provide consent were excluded from participation.

2.3. Study design and group definitions

The study included four distinct groups: patients admitted to the ward with a diagnosis of bronchiolitis (Group 1), patients admitted to the ward with a diagnosis of mild to moderate pneumonia (Group 2), patients with a diagnosis of severe pneumonia (Group 3), and the control group (Group 4). The Pediatric Infectious Diseases Society and the Infectious Diseases Society of America's guideline for children over 3 months of age was used for the severity of pneumonia [12].

A power analysis, based on data from a study by Mohamed et al., established a standard effect size of 0.95 [7]. The study's statistical power was calculated with a 5 % margin of error and 90 % power, considering a group size of 25 cases per group. Throughout the study period, a total of 202 eligible patients were admitted to the hospital. The flow of patients excluded due to exclusion criteria and lack of parental consent is illustrated in Fig. 1. Of the 72 eligible patients who visited the hospital for routine check-ups without active complaints, 26 consented to participate as the control group in the study. Consequently, a total of 75 patients and 26 controls were included in the study.

2.4. Data collection

Demographic and clinical characteristics, along with laboratory and imaging findings (chest radiography and thoracic computed tomography) at the time of presentation, were meticulously documented. All samples were taken on the day of admission. Standard assessments, including routine tests for C-reactive protein (CRP) and a complete blood count, were conducted across all groups. For patients in the study groups, additional data were collected, including lung imaging results, height and body weight measurements, presenting complaints, physical examination findings, procalcitonin levels, fibrinogen levels, and albumin values.

The diagnoses of community-acquired pneumonia and bronchiolitis were made by the same clinician using lung imaging and physical examination findings in accordance with the definitions of the Turkish Thoracic Society [13]. Anteroposterior lung imaging was conducted for each patient admitted to the hospital as a standard protocol.

Venous blood samples from study participants were collected in gel vacuum tubes and plastic tubes with K2 Ethylenediaminetetraacetic acid (EDTA) (BD, Plymouth, England). Samples in gel tubes were held at room temperature for 30 minutes, then centrifuged at 4000 g for 10 min., and separated into serum. On the sampling day, CRP, procalcitonin, and albumin tests were conducted using the Roche COBAS c701 device. Neutrophil and lymphocyte tests were run on the Sysmex XE-2100 device using EDTA tubes. Blood samples in BD Vacutainer sodium citrate tubes were immediately centrifuged at 1000xg for 15 min in a Beckman Coulter Allegra X-15R centrifuge, and fibrinogen was analyzed with the STAGO STA Compact Max device.

The fibrinogen-to-albumin ratio (FAR) was calculated as the fibrinogen value (g/L) divided by the albumin value (g/L). Similarly, the neutrophil-to-lymphocyte ratio (NLR) was determined by dividing the neutrophil value (/μL) by the lymphocyte value (/μL).

2.5. Serum Copeptin level measurement (Biomarker assay)

To explore the correlation between disease severity and copeptin levels, blood samples (0.5 ml) were obtained from the patients and subjected to centrifugation at 2700 rpm for 15 minutes following a 30-minute interval. The generated serum samples were then meticulously separated and preserved at −80°C for subsequent copeptin level analysis, with each sample being uniquely identified through a coding system known exclusively to the study investigators. Upon the conclusion of the recruitment phase, the cryopreserved samples were thawed and assessed for serum copeptin levels by a biochemist who remained unaware of the patient-sample correspondence. All patient data and test results were documented in an Excel file.

Approximately 40 μL of serum from each sample was analyzed utilizing the Human Copeptin Enzyme-Linked Immunosorbent Assay (ELISA) Kit from BT LAB (Bioassay Technology Laboratory), a product of Shanghai Korain Biotech Co., Ltd. (Shanghai, China) with the Elitech

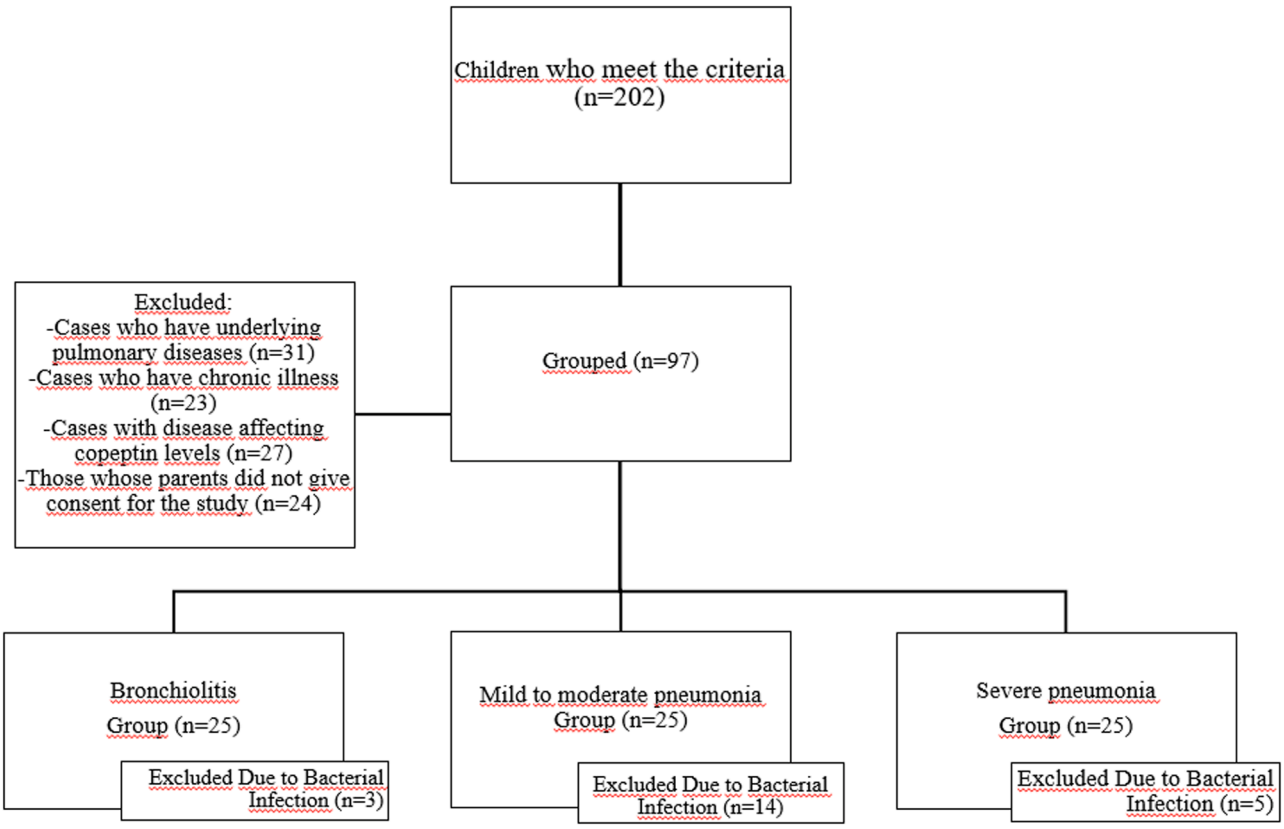

Fig. 1. Flowchart of the study.

ELx 800 device. The absorbance (optical density [OD]) of the samples was gauged at 450 nm using a microplate reader (Allsheng, #AMR-100, Hangzhou, China). Employing the concentrations of the standards and their corresponding OD readings, a standard curve with a linear regression equation and graph was produced. Subsequently, the samples' OD values were input into the regression equation to compute their concentrations. The measurement range spanned from 0.05 ng/ml to 5.0 ng/ml. The copeptin measurement protocol adhered strictly to the ELISA kit's instructions for use.

2.6. Masking

Participants were selected by a primary investigator who identified eligible patients according to the inclusion criteria, assigned them to groups, requested tests, and referred them to another researcher. This second researcher managed treatment and follow-up. A third researcher, blinded to group information, entered test results, including copeptin levels. A fourth researcher conducted statistical analyses, aware only that patients were labeled as groups 1, 2, 3, and 4 but blinded to their diseases. To prevent bias, researchers interpreting copeptin statistics matched groups with diseases only after the analysis, ensuring that group assignments did not influence results.

2.7. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences software version 22.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to determine whether the variables were normally distributed. Numbers and percentages were used to express categorical variables. Means ± standard deviations or medians with interquartile ranges were used to express continuous variables, depending on whether they showed a parametric or nonparametric distribution. The chi-square test was used to compare categorical variables and the Student's t-test and Mann–Whitney U test to compare continuous variables between two groups, depending on the sample distribution. Independent comparisons of more than two groups were conducted using the Kruskal–Wallis test when the data were not normally distributed. Subgroup analyses were performed using the Mann–Whitney U test, and the findings were interpreted with the Bonferroni correction. When both parameters were normally distributed, correlation coefficients and their significance were calculated using the Pearson test; otherwise, the Spearman test was used. A 5 % type I error level was used to infer statistical significance. A p-value of <0.05 was considered significant. Post hoc analysis was used to assess statistical differences between two groups. Factors determining the receiver operating characteristic (ROC) curve by group were analyzed using logistic regression. The capacity of copeptin, procalcitonin, NLR, FAR, and CRP levels to predict a severe clinical course was analyzed using ROC curve analysis. For each parameter, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative LR (LR−), accuracy, and area under the ROC curve (AUC) were calculated as diagnostic tools for predicting a moderate-to-severe clinical course. When evaluating the AUC, a 5 % type I error level was used to define a statistically significant predictive value of the test variables. Cut-off values were analyzed by ROC curve analysis.

2.8. Ethics approval

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the University of Medical Sciences Istanbul Haseki Training and Research Hospital Institutional Review Board. Ethics committee approval for this study was obtained from the Clinical Research Ethics Committee of University of Medical Sciences Istanbul Haseki Training and Research Hospital, under decision number 63-2023 dated April 04, 2023. Informed consent was obtained from the parents of all children enrolled in this study.

3. Results

3.1. Patient demographic characteristics, physical examination findings, and laboratory values

The median age of all patients included in the study (n=101) was 9 (25th–75th percentile: 3–18) months, and 58 (57.4 %) were male. A comprehensive comparison of the demographic characteristics, physical examination findings, and laboratory values of the groups is presented in Table 1. Subgroup analyses of the values showing statistically significant differences are given in Table 2.

3.2. Copeptin values

The copeptin levels of the groups are shown in Fig. 2. In subgroup analyses, the copeptin values exhibited statistically significant differences across all groups (***$P<0.001$ for all). The copeptin level exhibited a positive correlation with fibrinogen and FAR levels while demonstrating a negative correlation with albumin levels (r=0.354, **$P=0.002$; r=0.408, ***$P<0.001$; and r=−0.334, **$P=0.003$, respectively).

When patients requiring mechanical ventilation were categorized into two subgroups based on invasive and non-invasive support, no statistically significant difference was observed between them regarding copeptin values (1.86 [1.60-2.49] versus 1.62 [1.50-1.95], P=0.266).

3.3. Disease severity assessment using copeptin

ROC curves comparing the groups and associated data are depicted in Fig. 3 and summarized in Table 3. Copeptin demonstrated a sensitivity of 87.4 % and specificity of 82.2 % for distinguishing between patients with bronchiolitis and pneumonia, using a cut-off value of >0.586 ng/ml. Additionally, for the identification of patients with severe pneumonia versus those with mild to moderate pneumonia, copeptin exhibited a sensitivity of 97.9 % and specificity of 94.7 % with a cut-off value of >1.215 ng/ml.

4. Discussion

The principal finding of our study is the observed association between copeptin levels and disease severity in children with pneumonia. Notably, copeptin emerged as a more efficacious predictor of disease severity than other acute phase reactants. Copeptin is also an effective biomarker in the differentiation of bronchiolitis and pneumonia.

Acute phase reactants exhibited no significant differences between Groups 2 and 3; however, copeptin demonstrated a statistically significant difference across all groups. When compared with established severity indicators from previous studies, such as NLR [14–17] and FAR [17–19], copeptin emerged as a more robust predictor. While our study did not find a correlation between NLR and disease severity, a study in adults suggested a potential association between NLR and community-acquired pneumonia [20].

Copeptin appears to be a valuable marker for distinguishing patients with pneumonia. In a prior study, median copeptin levels were notably elevated in children with pneumonia when contrasted with those of healthy volunteers [6]. The current study substantiates and aligns with these findings, further supporting the potential utility of copeptin as a discriminatory parameter in pneumonia cases. Copeptin is recognized for its ability to reflect the severity of pneumonia and predict mortality in adults [21,22]. Furthermore, it has been linked to disease severity in adult patients diagnosed with coronavirus disease 2019 [23]. The copeptin level was found to be statistically significantly higher in pediatric pneumonia patients who passed away compared to those who survived, although it was not identified as an independent predictor of mortality [8]. In analogous studies, copeptin concentrations were noted to be markedly elevated in intensive care unit patients in comparison to control groups [10,24]. In our study, we observed a correlation between copeptin levels, the severity of pneumonia. However, we believe that further large-scale studies are warranted to establish a conclusive association between copeptin and mortality in pediatric cases. We also think that copeptin is an effective biomarker in the differentiation of bronchiolitis and pneumonia.

In congruence with our study, other investigations with similar findings employed ROC curve analysis, revealing an optimal cut-off point for plasma copeptin levels in predicting pneumonia that ranged between 0.436 and 0.527 ng/mL [7,10]. The calculated AUC values fell within the range of 0.62–0.87, indicating copeptin's potential as a biomarker for LRTI. These studies reported a high sensitivity of 85–89 % and a satisfactory specificity of 70–73 % [7,10]. Additionally, a positive predictive value of 91 % and a negative predictive value of 69 % were documented in one of the studies [10].

While our study identified a correlation between copeptin and FAR,

Table 1
Comparison of demographic characteristics, physical examination findings, and laboratory values of the groups.

		GROUP 1 Bronchiolitis	GROUP 2 Mild-Moderate pneumonia	GROUP 3 Severe pneumonia	GROUP 4 Control	P
Age (months)		11 (6,5 – 17)	8 (3 – 37,5)	8 (3 – 27,5)	16,5 (8 – 22)	0,726[b]
Sex (n, %)	Girl	12 (48,0)	11 (44,0)	9 (36,0)	12 (46,2)	0,836[c]
	Boy	13 (52,0)	14 (56,0)	16 (64,0)	14 (53,8)	
Fever		17 (68,0)	9 (36,0)	15 (60,0)		0,064[c]
Cough		25 (100,0)	25 (100,0)	23 (92,0)		0,324[c]
Respiratory Findings		7 (28,0)	9 (36,0)	19 (76,0)		<0,001[c]
Leukocyte (/uL)		12013 ± 3529	13010 ± 5588	14198 ± 6013	9003 ± 2341	0,001[a]
Neutrophil (/uL)		4550 (3170 – 7405)	5580 (3245 – 12475)	5710 (3175 – 9565)	3155 (2575 – 4670)	0,013[b]
Lymphocyte (/uL)		5250 (3520 – 6720)	3580 (2465 – 5480)	4520 (2415 – 8090)	4255 (2997 – 4977)	0,095[b]
NLR[d]		0,94 (0,53 – 1,52)	1,64 (0,56 – 2,03)	1,12 (0,55 – 2,99)	0,94 (0,63 – 1,19)	0,244[b]
C-reactive protein (mg/L)		6,5 (2,9 – 24,6)	14,4 (2,8 – 43,7)	18,4 (5,8 – 32,2)	2 (0,3 – 3,5)	<0,001[b]
Procalcitonin (ug/L)		0,06 (0,02 – 0,12)	0,11 (0,05 – 0,60)	0,21 (0,07 – 0,65)		0,005[b]
Fibrinogen (g/L)		2,4 (2,20 – 2,55)	3,43 (2,73 – 4,87)	3,2 (2,95 – 3,70)		<0,001[b]
Albumin (g/L)		44 (41 – 46)	40 (38 – 42,5)	39 (34 – 41)		<0,001[b]
FAR[e]		0,053 (0,048 – 0,062)	0,084 (0,065 – 0,117)	0,089 (0,077 – 0,104)		<0,001[b]
Copeptin (ng/ml)		0,641 (0,562 – 0,724)	0,846 (0,695 – 1,043)	1,624 (1,511 – 1,958)	0,461 (0,353 – 0,555)	<0,001[b]

All values are presented either as mean ± standard deviation or as median (25th-75th percentile).
[a] One-Way ANOVA test,
[b] Kruskal Wallis Test,
[c] Chi square test
[d] NLR: neurophil lymphocyte ratio,
[e] FAR: fibrinogen lymphocyte ratio

Table 2
Subgroup analyses of laboratory values.

	GROUP 1 vs.			GROUP 2 vs.		GROUP 3 vs.
	Group 2 p	Group 3 p	Group 4 p	Group 3 p	Group 4 p	Group 4 p
Leukocyte*	0.874	0.409	**0.005**	0.887	**0.012**	**0.002**
Neutrophil **	0.342	0.265	0.023	0.923	0.016	**0.004**
C-reactive protein**	0.473	0.101	**<0.001**	0.541	**<0.001**	**<0.001**
Copeptin**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Procalcitonin†	0.022	**0.002**		0.382		
Fibrinogen†	**<0.001**	**<0.001**		0.771		
Albumin†	**0.001**	**<0.001**		0.195		
Fibrinogen Albumin Ratio†	**<0.001**	**<0.001**		0.741		

Bonferroni correction,
* p<0.05,
** p<0.0083,
† p<0.017

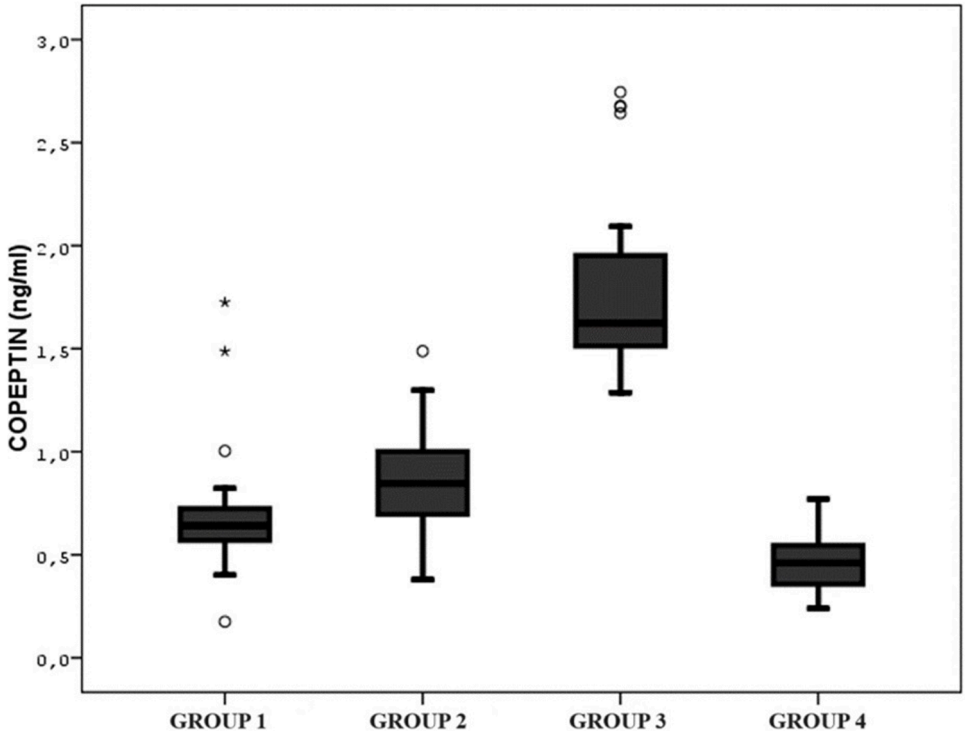

Fig. 2. Copeptin levels of the groups.

the predictive power of copeptin surpassed that of FAR in assessing pneumonia severity. These findings collectively suggest that copeptin may serve as a robust predictor of disease severity. While CRP effectively distinguished between bronchiolitis and pneumonia, and procalcitonin, as well as FAR, accurately predicted severe pneumonia, it is noteworthy that none demonstrated the same level of potency and reliability as copeptin. Studies conducted during the neonatal period have identified a correlation between respiratory support and copeptin levels [25,26]. In our study, although copeptin levels increased in the patients' requiring ventilators, no significant difference was detected between patients receiving invasive and non-invasive ventilator support. It is noteworthy that the sample size in these subgroups is limited, and we acknowledge the necessity for a larger cohort of patients to draw more definitive conclusions. However, to the best of our knowledge, there is no pediatric study examining the association between copeptin and the requirement for invasive and non-invasive mechanical ventilation.

In children with LTRI at presentation, copeptin measurement can provide a preliminary assessment of disease severity, helping differentiate between bronchiolitis and pneumonia and predict the disease course. Early diagnosis and accurate treatment can lead to faster recovery, shorter hospital stays, and more efficient decision-making for physicians. Copeptin may offer these advantages over other acute-phase markers. While studies on copeptin have mainly focused on community-acquired pneumonia and its complications, we found no research on its use in distinguishing bacterial from non-bacterial pneumonia [6–11,27,28]. We believe our study could serve as a reference for future research, and larger studies are needed to confirm these findings.

A recent study indicates that copeptin values decrease as the day progresses during the course of the illness [29]. While blood tests were conducted on all our patients upon admission, the inability to precisely ascertain the duration of patients' symptoms and findings, coupled with the absence of control copeptin tests during follow-up, represents a limitation in the robustness of our study. Since an extra tube of blood was required for the study, the high rate of families not consenting to participate (especially in the control group) can be considered a limitation in our study. The study also has other limitations, including its

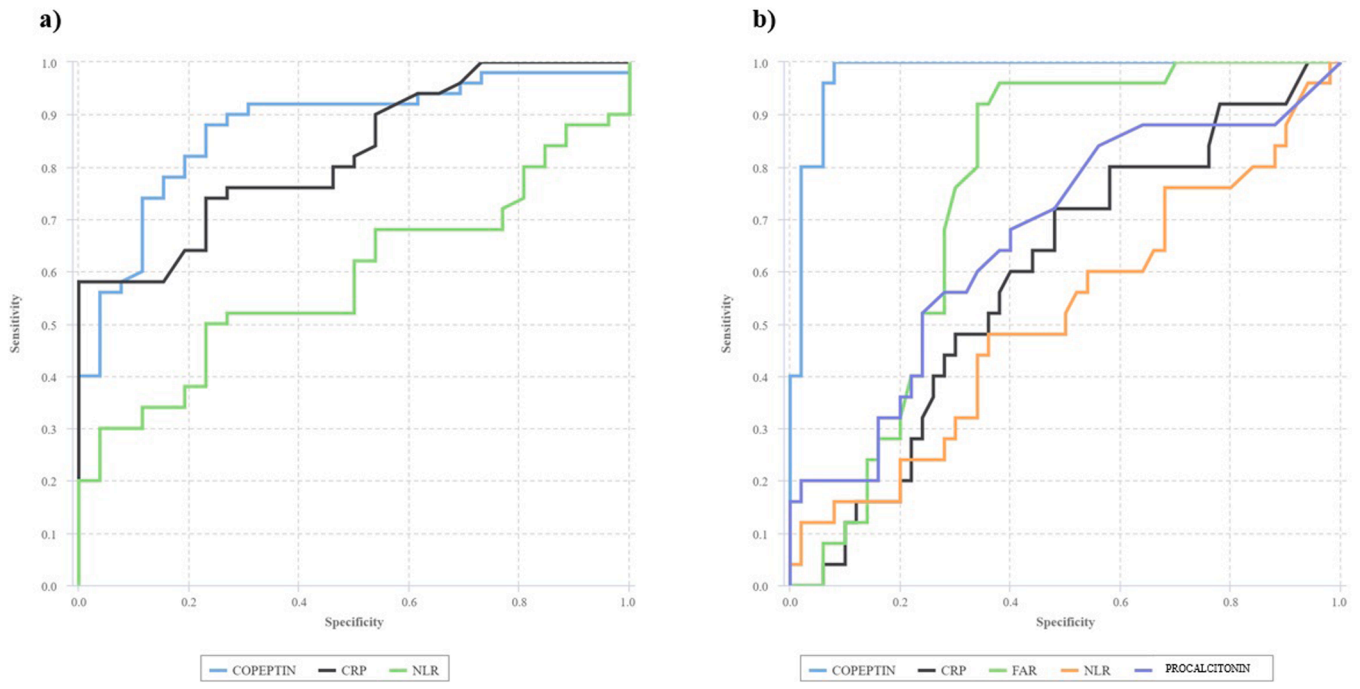

Fig. 3. a: Receiver operating characteristic (ROC) curve analysis comparing copeptin levels between bronchiolitis (Group 1) and pneumonia (Group 2 + Group 3) subjects
b: Receiver operating characteristic (ROC) curve analysis comparing copeptin levels between the mild to moderate pneumonia (Group 2) and severe pneumonia (Group 3) groups.

Table 3
Information about the receiver operating characteristic (ROC) curve.

	Bronchiolitis vs Pneumonia			*Mild-Moderate Pneumonia vs Severe Pneumonia*				
	Copeptin	*CRP*[a]	*NLR*[b]	*Copeptin*	*CRP*[a]	*NLR*[b]	*PCT*[c]	*FAR*[d]
AUC[e]	0.874	0.825	0.585	0.979	0.593	0.514	0.664	0.750
95 % CI[f]	0.778–0.939	0.720–0.903	0.446–0.697	0.916–0.998	0.473–0.705	0.396–0.632	0.545–0.769	0.637–0.843
Sensitivity	87.4 %	82.5 %	58.5 %	97.9 %	59.3 %	51.4 %	66.4 %	75.0 %
Specificity	82.2 %	76.4 %	52.9 %	94.7 %	57.5 %	50.8 %	60.7 %	73.4 %
LR+[g]	4.91	3.50	1.24	18.4	1.40	1.04	1.69	2.82
LR-[h]	0.15	0.23	0.78	0.02	0.71	0.96	0.55	0.34
PPV[i]	82.9 %	77.4 %	55.2 %	95.1 %	57.8 %	50.5 %	62.3 %	73.5 %
NPV[j]	86.3 %	80.9 %	55.8 %	97.9 %	58.2 %	50.5 %	63.8 %	74.5 %
Accuracy	84.5 %	79.5 %	56.0 %	96.5 %	58.5 %	51.0 %	63.5 %	74.0 %
Cut-off value	>0.586 ng/mL	>5.7 mg/L		>1.215 ng/mL			>0.17 g/L	>0.084
P	<0.001	<0.001	0.191	<0.001	0.176	0.845	<0.001	<0.001

[a] CRP: C-reactive protein,
[b] NLR: Neutrophil lymphocyte ratio,
[c] PCT: Procalcitonin,
[d] FAR: Fibrinogen albumin ratio,
[e] AUC: Area under the curve,
[f] CI: Confidence interval,
[g] LR+: Positive likelihood ratio,
[h] LR-: Negative likelihood ratio,
[i] PPV: Positive predictive value,
[j] NPV: Negative predictive value

single-center nature, the inability to identify the specific causative agent of pneumonia for each patient, and the inherent challenge of comprehensively understanding all the factors influencing copeptin. Despite the implementation of exclusion criteria targeting diseases known to alter copeptin levels, the full spectrum of factors affecting copeptin remains uncertain due to the novelty of the molecule and the limited availability of existing research. While the present study was structured as a prospective case-control study, the substantiation of our findings requires larger sample sizes, the inclusion of outpatient pneumonia cases, and the implementation of a multicenter approach with long-term follow-up assessments. In particular, the present findings are worthy of further validation in a larger pediatric cohort to define the cut-off value for identifying patients at a high risk of more severe respiratory disease.

5. Conclusions

Copeptin demonstrates potential as a predictor of disease severity in children with pneumonia. It can also serve as a valuable tool to guide physicians in differentiating between bronchiolitis and pneumonia, as well as in diagnosing severe pneumonia. Furthermore, our study

indicates that copeptin may outperform other acute phase reactants such as NLR, FAR, CRP, and procalcitonin in signaling the severity of the disease.

Disclosures and representations

Financing

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ClinicalTrials

The study was registered on ClinicalTrials.gov (NCT06211985).

Availability of data and methods

The authors confirm that data supporting the findings of this study are available within the article. Other data in this study are available from the corresponding author upon reasonable request.

Ethics approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approved by the Institutional Review Board.

Ethics committee approval for this study was obtained from the Health Sciences University, Haseki Training and Research Hospital, Clinical Research Ethics Committee under decision number 63-2023 dated April 04, 2023. Informed consent was obtained from the parents of all children enrolled in this study.

Informed consent

Informed consent forms were obtained from the parents of the patients.

Publication permission

All authors declare that they approve the final version of the manuscript and allow it to be published.

CRediT authorship contribution statement

Berker Okay: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Halil Ugur Hatipoglu:** Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Zeynep Uze Okay:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cevher Kızılırmak:** Writing – review & editing, Validation, Methodology, Investigation, Data curation, Conceptualization. **Ahsen Guler:** Writing – original draft, Resources, Methodology, Formal analysis, Conceptualization. **Kâmil Sahin:** Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Gulsen Akkoc:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Evers KS, Wellmann S. Arginine Vasopressin and copeptin in perinatology. Front Pediatr 2016;4:75.
[2] Katan M, Christ-Crain M. The stress hormone copeptin: a new prognostic biomarker in acute illness. Swiss Med Wkly 2010;140:13101.
[3] WHO. Global Health Observatory resources, mortality and global health estimates. [Access Date 12.12.2023]. Available from: https://www.who.int/gho/child_health/mortality/mortality_under_five/en/.
[4] Christ-Crain M, Morgenthaler NG, Stolz D, Müller C, Bingisser R, Harbarth S, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. Crit Care 2006;10(3):R96.
[5] Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem 2006;52(1):112–9.
[6] Du J-M, Sang G, Jiang C-M, He X-J, Han Y. Relationship between plasma copeptin levels and complications of community-acquired pneumonia in preschool children. Peptides 2013;45:61–5.
[7] Mohamed GB, Saed MA, Abdelhakeem AA, Salah K, Saed AM. Predictive value of copeptin as a severity marker of community-acquired pneumonia. Electr Phys 2017;9(7):4880–5.
[8] Abdel-Fattah M, Meligy B, El-Sayed R, El-Naga YA. Serum copeptin level as a predictor of outcome in pneumonia. Indian Pediatr 2015;52(9):807–8.
[9] Alcoba G, Manzano S, Lacroix L, Galetto-Lacour A, Gervaix A. Proadrenomedullin and copeptin in pediatric pneumonia: a prospective diagnostic accuracy study. BMC Infect Dis 2015;15:347.
[10] Wrotek A, Jackowska T, Pawlik K. Sodium and copeptin levels in children with community acquired pneumonia. Adv Exp Med Biol 2015;835:31–6.
[11] Leung AKC, Wong AHC, Hon KL. Community-acquired pneumonia in children. Recent pat inflamm allergy drug discov. 2018;12(2):136-44. doi:10.2174/1872213X12666180621163821.
[12] Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the pediatric infectious diseases society and the infectious diseases society of America. Clin Infect Dis 2011;53(7):e25–76. https://doi.org/10.1093/cid/cir531.
[13] Türk Toraks Derneği Çocuklarda Toplumda Gelişen Pnömoni Tanı ve Tedavi Uzlaşı Raporu. Türk Toraks Derneği 2023;5–40. [Access Date 04.12.2024]. https://toraks.org.tr/site/sf/books/2023/12/771b2ce640645948509601bdb319116622032cba0e00afd66955e38c35275bc3.pdf.
[14] Jiang J, Liu R, Yu X, Yang R, Xu H, Mao Z, et al. The neutrophil-lymphocyte count ratio as a diagnostic marker for bacteraemia: A systematic review and meta-analysis. The Am J Emerg Med 2019;37(8):1482–9.
[15] Rasyid H, Sangkereng A, Harjianti T, Soetjipto AS. Impact of age to ferritin and neutrophil-lymphocyte ratio as biomarkers for intensive care requirement and mortality risk in COVID-19 patients in Makassar, Indonesia. Physiol Rep. 2021;9(10):4–10.
[16] Shusterman E, Prozan L, Ablin JN, Weiss-Meilik A, Adler A, Choshen G, et al. Neutrophil-to-lymphocyte ratio trend at admission predicts adverse outcome in hospitalized respiratory syncytial virus patients. Heliyon 2023;9(6):e16482.
[17] Okay ZU, Okay B, Hatipoglu HU, Akkoc G, Sahin K. The association of fibrinogen-albumin ratio and neutrophil-lymphocyte ratio with the severity of respiratory syncytial virus infection in children. Rev Inst Med Trop Sao Paulo 2024;66:e26.
[18] Küçükceran K, Ayranci MK, Girişgin AS, Koçak S. Predictive value of D-dimer/albumin ratio and fibrinogen/albumin ratio for in-hospital mortality in patients with COVID-19. Int J Clin Pract 2021;75(7):1–6.
[19] Kayapinar O, Ozde C, Kaya A. Relationship between the reciprocal change in inflammation-related biomarkers (Fibrinogen-to-Albumin and hsCRP-to-Albumin Ratios) and the presence and severity of coronary slow flow. Clin Appl Thromb Hemost 2019;25(1):1–10.
[20] Curbelo J, Luquero Bueno S, Galván-Román JM, Ortega-Gómez M, Rajas O, Fernández-Jiménez G, et al. Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio. PLoS One 2017;12(3):e0173947.
[21] Kolditz M, Halank M, Schulte-Hubbert B, Bergmann S, Albrecht S, Höffken G. Copeptin predicts clinical deterioration and persistent instability in community-acquired pneumonia. Respir Med 2012;106(9):1320–8.
[22] Christ-Crain M, Schuetz P, Müller B. Biomarkers in the management of pneumonia. Expert Rev Respir Med 2008;2(5):565–72.
[23] Hammad R, Elshafei A, Khidr EG, El-Husseiny AA, Gomaa MH, Kotb HG, et al. Copeptin: a neuroendocrine biomarker of COVID-19 severity. Biomark Med 2022;16(8):589–97.
[24] Jochberger S, Mayr VD, Luckner G, Wenzel V, Ulmer H, Schmid S, et al. Serum vasopressin concentrations critically ill patients. Crit Care Med 2006;34(2):293–9.
[25] Evers KS, Wellmann S. Arginine Vasopressin and copeptin in perinatology. Front Pediatr 2016;4:75. https://doi.org/10.3389/fped.2016.00075. Published 2016 Aug 2.
[26] Benzing J, Wellmann S, Achini F, Letzner J, Burkhardt T, Beinder E, et al. Plasma copeptin in preterm infants: a highly sensitive marker of fetal and neonatal stress. J Clin Endocrinol Metab 2011;96(6):E982–5. https://doi.org/10.1210/jc.2010-2858.
[27] To KK, Lee KC, Wong SS, Sze KH, Ke YH, Lui YM, et al. Lipid metabolites as potential diagnostic and prognostic biomarkers for acute community acquired

pneumonia. Diagn Microbiol Infect Dis 2016;85(2):249–54. https://doi.org/10.1016/j.diagmicrobio.2016.03.012.

[28] Moustafa AN, Moness HM, Ali MWE. Red cell distribution width as a prognostic marker for complications of community-acquired pneumonia in children: a comparison with Proadrenomedullin and Copeptin. BMC Pulm Med 2023;23(1):371. https://doi.org/10.1186/s12890-023-02686-z.

[29] Baumann P, Fuchs A, Gotta V, Ritz N, Baer G, Bonhoeffer JM, et al. The kinetic profiles of copeptin and mid regional proadrenomedullin (MR-proADM) in pediatric lower respiratory tract infections. PLoS One 2022;17(3):e0264305.