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Original article

The Value of Pentraxin-3 (PTX-3) as Clinical Marker in Diagnosis of Pediatric Community Acquired Pneumonia (CAP)

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Abstract:

Background: Community acquired pneumonia (CAP) is defined as the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital. This study aimed to evaluate the value of pentraxin-3 (PTX-3) as a clinical marker in the diagnosis of CAP in pediatrics and assessment of its severity. **Methods:** This cross-sectional study included 60 children, divided into 40 children with CAP and 20 age and sex-matched healthy controls. All the patients underwent general and chest examination, laboratory investigations, and radiological examination. **Results:** The PTX3 levels showed statistically significant positive correlation with the WBCs count ($r = 0.285$, $p = 0.027$), neutrophils count ($r = 0.259$, $p= 0.046$), erythrocytic sedimentation rate ($r = 0.486$, $p < 0.001$), hospital stay length ($r = 0.465$, $p = 0.003$), C-reactive protein ($r = 0.365$, $p = 0.004$), and hematocrit value ($r = 0.372$, $p = 0.003$). PTX3 level of 7.94 (ng/ml) wase able to differentiate patients with CAP from the control group with a sensitivity of 95% and a specificity of 95%. PTX3 level had a significantly higher diagnostic performance for discrimination of CAP patients compared to CRP ($p =0.041$) and procalcitonin PCT (0.03). **Conclusion:** PTX3 emerges as a promising biomarker for CAP diagnosis and severity assessment, exhibiting potential advantages over conventional markers like CRP and PCT. The findings highlight the clinical utility of PTX-3 in discriminating CAP from controls with high sensitivity and specificity.

Keywords: PTX-3, Marker, Pediatric, Community Acquired Pneumonia.

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Introduction

Pneumonia is defined as inflammation and consolidation of the lung tissue commonly due to an infectious agent. Pneumonia that develops outside the hospital is considered community acquired pneumonia (CAP) [(1)]. CAP is also defined as the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital. CAP is one of the most common serious infections in children [(2)]. CAP remains a common and serious illness despite the availability of new and potent antibiotics and effective vaccines. It is, moreover, one of the main causes of death in children, especially in developing countries. The understanding of CAP is rapidly expanding and the ability to prevent and treat the disease has improved in recent years [(3).]

Despite advances in diagnosis and treatment, CAP remains a common, potentially fatal disease associated with significant morbidity, mortality, and health care expenditure. In patients with CAP requiring ICU admission, mortality may involve more than half of these patients compared with 4–18% mortality in ward admission and only less than 1% who do not need hospitalization [(2)].

Although the diagnosis of CAP is suggested by clinical features such as fever, cough and respiratory distress, chest radiography is the gold standard for confirming the diagnosis and for severity assessment. However, current guidelines recommend that chest radiography should not be considered a routine investigation in children thought to have CAP. So, it could be useful to identify serum markers that could predict pulmonary involvement in order to stratify children who should undergo further radiographic investigation [(4)].

Pentraxin-3 (PTX-3) is an acute inflammatory protein that was discovered in recent years. It belongs to the long pentraxins family, which is a superfamily of the C-reactive protein (CRP). PTX3 can be detected at the infected site within a few hours after infection, and the plasma PTX3 level is correlated with the severity of various infectious diseases [(5)]. PTX-3 is a novel marker that behaves as an acute-phase protein as its blood levels, which are low in normal conditions, rapidly increase in the plasma during inflammation. PTX-3 is released in response to microbial recognition and can bind specific pathogens such as fungi, bacteria, and viruses [(6)].

The purpose of this study was to evaluate the value of PTX-3 as a clinical marker in the diagnosis of CAP in pediatrics and assessment of its severity.

Subjects and Methods

This cross-sectional case-control study included 60 subjects at the pediatric department of Benha University Hospital during the period from 1st May to 31st October 2022 who were eligible for the study with parents' agreement to participate in the study.

An informed written consent was obtained from the parents of the study subjects. They received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University.

Inclusion criteria were children from the inpatient pediatric department or outpatient clinic of Benha University Hospitals, diagnosed to have pneumonia, according to WHO, 2019 [(1)]. According to these guidelines, the criteria for diagnosing pneumonia in children are: cough with difficulty breathing and tachypnea, lower chest wall indrawing, absence of stridor and children aged between 1 month and 12 years.

Exclusion criteria were patients with chronic diseases other than pneumonia as

cardiovascular diseases, perinatal abnormality, immunodeficiency, other pulmonary disease and patients on immunosuppressants.

Grouping:

This study included 40 children with CAP and 20 age and sex-matched healthy children as a control group.

All the studied patients were subjected to the following: Full history taking, including personal history (age, gender), medical history (any chronic disease such as diabetes mellitus, hypertension, medications, and drug allergy), history of the present illness (fever, cough, fatigue, malaise, body aches)]. **Clinical examination: general examination including** level of consciousness and complexion, vital signs (heart rate, respiratory rate, blood pressure and temperature), signs of respiratory distress, lower limb edema, anthropometric measurement (weight, height and BMI). **Chest examination:** general inspection, chest palpation, percussion**,** auscultation and cough assessment.

Laboratory investigations:

Complete blood count (CBC): CBC was done using SysmexKX-21N, Sysmex Corporation, New York, USA to estimate hemoglobin level and blood indices (MCV, MCH, MCHC and RDW). Then **blood films** were prepared and stained by Leishman's stain for differential count. **C-reactive protein (CRP):** CRP was estimated using a rapid latex agglutination test for qualitative screening and semi-quantitative determination of serum CRP at 340 nm by a turbidimetric method. The expected normal CRP value was <6 mg/L. **Procalcitonin (PCT):** PCT levels were measured through a chemiluminescent immunoassay (CLIA) method. **Serum pentraxin -3 (PTX-3) analysis (ng/ml):** The analysis was done using Pentraxin -3 enzyme-linked immunosorbent assay (ELISA) kit (sun red technology company – Shanghai-China. The entire kit was stored at -20°C until use.

Radiological examination:

Computed tomographic (CT) scan of the chest: The patients were scanned in a supine position with the arms above the head to avoid artifacts. Image acquisition was at 1.25 mm thickness, 0.625 mm interval using 512 × 512 matrix, tube speed 35 mm/rotation with 0.5 s rotation time. The kVp and mAs was used as low as possible controlled by the operator before scanning to get low radiation doses as possible. The images were transferred to the workstation for reviewing the axial slices along with multi-planar reformation. The images were interpreted by experienced radiologists blinded to the patients' diagnosis.

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Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 28.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR) accordingly. Correlation analysis was done using Pearson test to determine the correlation between the PTX-3 and the patients' characteristics. Significance of the obtained results was judged at the 5% level.

Results

No statistically significant difference was detected between the two groups regarding sex and age. The history of recurrence and hospitalization, previous history and symptoms, clinical presentation, complications and hospital stay of the studied patients are demonstrated in **Table 1**

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Compared with the controls, children in the patients' group had significantly higher WBCs count, neutrophil count, relative percentage of neutrophils, the 1st hour ESR, CRP, PCT, and PTX3 levels (P<0.05), and significantly lower relative percentage of lymphocytes (p < 0.001). **Table 2**

Table 1: Demographic and clinical data, complications and hospital stay of the studied groups

Demographic and clinical data		CAP (n = 40)		Control (n = 20)		Test of Sig.	P value
		No.	**%**	**No.**	**%**		
Gender							
Female		14	35.0%	8	40.0%	χ^2= 0.144	0.705
Male		26	65.0%	12	60.0%		
Age (years)							
Min. – Max.		0.25 – 11.0		0.2 – 11.0		t=	0.929
Mean ± SD.		4.59 ± 3.02		4.67 ± 2.93		-0.09	
Median (IQR)		3.8 (2.48 – 6.25)		4.31 (2.8 – 5.53)			
Clinical history and symptoms							
History of recurrence		10	25.00%	------		------	------
History of hospitalization		5	12.50%	------		------	------
Fever		18	45.00%	------		------	------
Duration of fever (days)	**Min. – Max.**	0.5 – 4.0		------		------	------
	Mean ± SD.	2.21 ± 0.97		------		------	------
	Median (IQR)	2 (1.75 – 3.0)		------		------	------
Peak of temperature (°C)	**Min. – Max.**	36.2 – 39.2		------		------	------
	Mean ± SD.	37.38 ± 0.72		------		------	------
	Median (IQR)	37.2 (36.9 – 39.2)		------		------	------
Cough		40	100.00%	------		------	------
Restlessness		4	10.00%	------		------	------
Tachypnea		39	97.50%	------		------	------
Tachycardia		20	50.00%	------		------	------
Clinical presentation							
Pallor		8	20.00%	------		------	------
Cyanosis		2	5.00%	------		------	------
Respiratory distress (RD)		19	47.50%	------		------	------
Grade of RD	**I**	10	------	------		------	
	II	5	------	------		------	
	III	4	------	------		------	
Reduced O2 saturation		10	25.00%	------		------	------
Reduced air entry		9	22.50%	------		------	------
Wheezes		5	12.50%	------		------	------
Crepitations		15	37.50%	------		------	------
Complications							
Lung collapse		1	2.5%	------		------	------
Pleural effusion		2	5.00%	------		------	------
Necrotizing pneumonia		1	2.5%	------		------	------
Length of hospital stay (days)	**Min. – Max.**	2 – 12		------		------	------
	Mean ± SD.	5.63 ± 3.02		------		------	------
	Median (IQR)	5 (3.75 – 7.25)		------		------	------

IQR: Inter quartile range, SD: Standard deviation, t: Student t-test, χ^2: Chi square test, p: p value for comparing between the two studied groups.

Table 2: Comparison between patients and control group according to the laboratory data

Laboratory data	CAP (n = 40)	Control (n = 20)	t	P value
WBCs (*10^3)	11.21 ± 4.67	5.97 ± 1.74	4.84	<0.001*
Lymphocytes(*10^3)	2.15 ± 0.91	1.81 ± 0.42	1.67	0.056
Lymphocytes	21.0 ± 10.0	32.0 ± 7.0	-4.56	<0.001*
Neutrophils(*10^3)	6.06 ± 2.31	2.81 ± 1.15	3.72	<0.001*
% Neutrophils	54.0 ± 11.0	47.1 ± 9.0	2.51	0.023*
ESR (mm/hr)	26.9 ± 22.87	4.8 ± 1.96	6.24	<0.001*
CRP (mg/L)	9.96 ± 5.75	1.12 ± 0.7	6.82	<0.001*
PCT (ng/mL)	0.85 ± 0.28	0.38 ± 0.12	7.21	<0.001*
PTX3 (ng/ml)	28.46 ± 17.67	4.31 ± 2.4	6.06	<0.001*

WBCs: white blood cells, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, PCT: procalcitonin, PTX3: pentraxin -3, IQR: Inter quartile range, SD: Standard deviation, t: Student t-test, □2: Chi square test, p: p value for comparing between the two studied groups, *: Statistically significant at $p \leq 0.05$

Comparison of the PTX3 levels according to the patients' characteristics showed that there were statistically significant differences in the PTX3 levels according to the grade of RD, with grade III patients showing significantly higher PTX3 levels compared to patients with grade I RD (p<0.001). Also, patients with lung complications had significantly higher PTX3 levels compared to those without (p <0.001). **Table 3**

The CRP levels showed statistically significant negative correlation with the relative percentage of lymphocytes (r = -0.318, p = 0.013) and statistically significant positive correlation with the ESR levels (r = 0.345, p = 0.007). The PCT levels showed statistically significant positive correlation with the WBCs count (r = 0.449, p < 0.001), neutrophils count (r = 0.393, p = 0.002), ESR (r = 0.54, p < 0.001), and CRP (r = 0.283, p = 0.029) and statistically significant negative correlation with the relative percentage of lymphocytes (r = -0.342, p = 0.007). The PTX3 levels showed statistically significant positive correlation with the WBCs count (r = 0.285, p = 0.027), neutrophils count (r = 0.259, p= 0.046), ESR (r = 0.486, p < 0.001), hospital stay length (r = 0.465, p = 0.003), CRP (r = 0.365, p = 0.004), and PCT (r = 0.372, p = 0.003). **Table 4**

CRP level of 5.24 (mg/L) was able to differentiate patients with CAP from the control group with a sensitivity of 72.5% and a specificity of 95%. PCT level of 0.51 (ng/mL) was able to differentiate patients with CAP from the control group with a sensitivity of 85% and a specificity of 90%. PTX3 level of 7.94 (ng/ml) wase able to differentiate patients with CAP from the control group with a sensitivity of 95% and a specificity of 95%. PTX3 had significantly higher diagnostic performance for discrimination of CAP cases compared to CRP (p =0.041) and PCT (0.03). **Figure 1**

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Table 3: Comparison of the PTX3 levels according to the patients' characteristics

CAP (n = 40)	PTX3 (ng/ml)	Test of significance	P value
Gender			
Female	16.4 ± 15	t = -0.13	0.199
Male	22.7 ± 20		
History of fever			
No	27.2 ± 19.5	t = -0.491	0.626
Yes	22.7 ± 15.6		
History of recurrence			
No	28.6 ± 18.3	t = 0. 06	0.956
Yes	28.2 ± 16.6		
History of hospitalization			
No	28.6 ± 17.5	t = 0.289	0.774
Yes	28.2 ± 20.7		
Restlessness			
No	27.4 ± 17.3	t = -1.12	0.272
Yes	37.8 ± 21.3		
Tachycardia			
No	27.4 ± 20.1	t = -0.363	0.719
Yes	29.5 ± 15.4		
Pallor			
No	29.7 ± 19.0	t = 0.853	0.399
Yes	23.7 ± 10.2		
Cyanosis			
No	29.1 ± 17.8	t = 0.950	0.348
Yes	16.9 ± 10.9		
Respiratory distress (RD)			
No	22 ± 12.5	t = -2.61	0.013*
Yes	35.6 ± 20		
Grade of RD			
I	24 ± 8.25	F= 0.144	P < 0.001*, p1= 0.173, p2 < 0.001*, P3= 0.148
II	39.6 ± 26.7		
III	59.5 ± 5.1		
Reduced O2 saturation			
No	29.2 ± 18.8	t = 0.780	0.440
Yes	25.8 ± 13.7		
Reduced air entry			
No	29.7 ± 18.3	t = 0.504	0.617
Yes	24.7 ± 15.7		
Wheezes			
No	26.6 ± 15.4	t = -1.81	0.078
Yes	41.5 ± 27.6		
Crepitations			
No	29.2 ± 18.3	t = 0.348	0.730
Yes	27.2 ± 17.1		
Lung complications			
No	37.8 ± 22.5	t = -5.49	< 0.001*
Yes	50.3 ± 9.9		

SD: Standard deviation, t: Student t-test, F: ANOVA test, p: p value for comparing between the studied groups, p1: patients with grade I RD vs. patients with grade II RD, p2: patients with grade I RD vs. patients with grade III RD, p3: patients with grade II RD vs. patients with grade III RD, *: Statistically significant at p ≤ 0.0

Table 4: Correlation of the CRP, PCT, and PTX3 levels with the numerical data of the studied patients

Patients' data	CRP (mg/L)		PCT (ng/mL)		PTX3 (ng/ml)	
	r	**p-value**	**r**	**p-value**	**r**	**p-value**
Age	-0.015	0.907	-0.04	0.759	-0.015	0.911
Fever duration	0.075	0.646	-0.012	0.94	0.232	0.15
Peak temperature	0.056	0.73	-0.08	0.834	0.201	0.215
WBCs count	0.206	0.115	0.449	< .001*	0.285	0.027*
Neutrophiles count	0.161	0.218	0.393	0.002*	0.259	0.046*
%Neutrophiles	-0.204	0.118	-0.174	0.185	-0.149	0.256
Lymphocytes count	0.011	0.932	0.213	0.103	0.149	0.256
% lymphocytes	-0.318	0.013*	-0.342	0.007*	-0.177	0.176
ESR	0.345	0.007*	0.54	< .001*	0.486	< .001*
Hospital stay length	0.013	0.935	-0.129	0.429	0.465	0.003*
CRP (mg/L)	---	---	0.283	0.029*	0.365	0.004*
PCT (ng/mL)	---	---	---	---	0.372	0.003*

WBCs: white blood cells, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, PCT: procalcitonin, PTX3: pentraxin -3, *: Statistically significant at $p \leq 0.05$

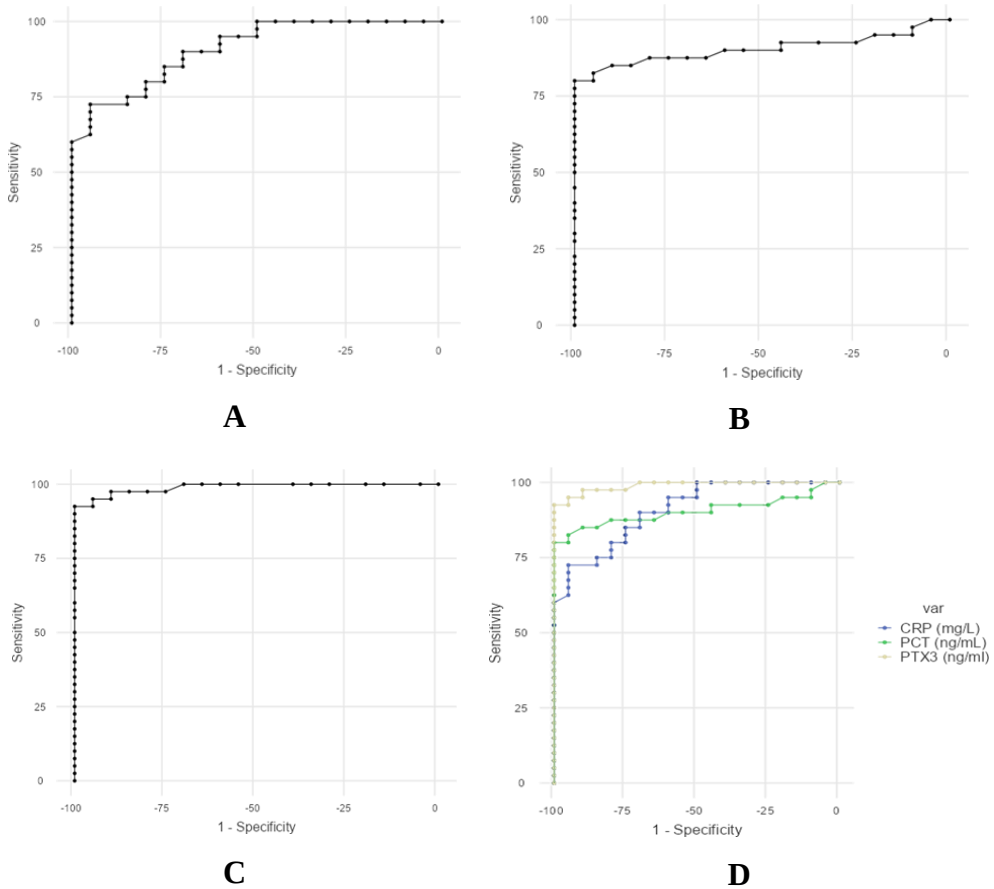

Figure 1: A: ROC curve analysis of CRP, B: ROC curve analysis for PCT, C: ROC curve analysis for the role of PTX3, D: Comparisons of the ROC curve analysis for the role of the three markers in the diagnosis of CAP

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Discussion

In recent years, there has been a growing interest in identifying reliable biomarkers to aid in the timely and accurate diagnosis of CAP in children. Among these biomarkers, PTX-3 has emerged as a promising candidate due to its role in the innate immune response and its potential as a marker of inflammation and tissue damage. Understanding the value of PTX-3 in the diagnosis of pediatric CAP is crucial for improving clinical management and outcomes in affected children [7].

Children in the patients group demonstrated significantly elevated white blood cell (WBC) counts compared to controls ($p < 0.001$). Furthermore, the patients group exhibited a significantly lower relative percentage of lymphocytes compared to controls ($p < 0.001$). Moreover, children with CAP displayed significantly higher neutrophil counts ($p < 0.001$) and a higher relative percentage of neutrophils ($p = 0.023$) compared to controls.

Our findings are consistent with the data published by Güven and colleagues [8] who observed the association of pediatric CAP with elevated WBCs count and relative neutrophils count. Likewise, Curbelo and colleagues [9] found that CAP was associated with increase in neutrophils and decrease in lymphocytes.

In the present study, patients with CAP demonstrated markedly higher CRP levels compared to controls ($p < 0.001$). In harmony with our findings, CRP was reported in the studies of Khan and colleagues [10] and Berg and colleagues [11] to be a much specific and sensitive indicator for CAP.

The current study demonstrated that pediatric patients with CAP exhibited significantly higher PCT levels compared to controls ($P < 0.001$). In agreement with our findings, Kim and colleagues [12] demonstrated a significant elevation of PCT levels in pediatric patients with CAP.

In the current work, pediatric patients with CAP exhibited markedly higher PTX3 levels compared to controls ($p < 0.001$). Data found in the literature are supporting our findings, where significantly elevated PTX3 levels were identified in the studies [12 , 5].

In our study, the comparison of PTX3 levels according to the patients' characteristics revealed significant associations between PTX3 levels and disease severity in pediatric CAP. Patients with respiratory distress demonstrated statistically significant differences in PTX3 levels according to the grade of respiratory distress. Grade III patients exhibited significantly higher PTX3 levels compared to patients with grade I RD. Moreover, patients with lung complications had significantly higher PTX3 levels compared to those without complications.

In another context, Zhou and colleagues [13] declared that the PTX3 level of patients with respiratory failure was higher than in the non-respiratory failure group and the difference was statistically significant. These findings are also consistent with previous studies on the prediction of infectious disease severity by the PTX3 level as shown in the study of Kao and colleagues [14]. Severe pneumonia and complications of pneumonia can cause a more robust systemic inflammatory response, causing the body to release more PTX3 into the blood when stimulated. This suggests a link between elevated PTX3 levels and the severity of respiratory compromise in pediatric CAP, highlighting the potential utility of PTX3 as a biomarker for assessing disease severity and guiding clinical management decisions.

Our study revealed that CRP levels demonstrated a statistically significant negative correlation with the relative percentage of lymphocytes. This underscores the dynamic interplay between the acute-phase inflammatory response and the cellular immune response in pediatric CAP. Secondly, CRP levels exhibited a statistically significant positive

correlation with ESR levels. Both CRP and ESR are acute-phase reactants produced in response to inflammation, and their levels rise concomitantly during acute infections.

In accordance with our study, Tyurin and colleagues [15] reported the significant negative association between the CRP levels and lymphocytes count and attributed this to that both conditions are associated with the systemic inflammatory conditions. Regarding the positive correlation between the CRP and ESR levels, the obtained results support the view of concomitant application of ESR and CRP in calculation of the disease activity indices in certain disorders, including CAP.

The current study showed that the PCT levels exhibited significant positive correlation with the WBCs count, neutrophils count, ESR, and CRP and statistically significant negative correlation with the relative percentage of lymphocytes. These correlations indicate a direct relationship between PCT levels and the acute-phase inflammatory response and further support the role of PCT as a sensitive marker of systemic inflammation and infection severity in pediatric CAP.

In a rather close context, Abedini and colleagues [16] highlighted the positive association of PCT with WBCs count, ESR, and CRP in children with systemic inflammatory response. They attributed this finding to the fact that, in severe inflammation, serum levels of PCT are noticeably elevated and levels of serum PCT correlate with the severity of the illness positively. This could explain the described associations with other inflammatory markers.

Nearly similar associations were found when the correlations of PTX3 levels with other parameters analyzed. Like PCT, the PTX3 levels showed statistically significant positive correlation with the WBCs count, neutrophils count, ESR, and CRP. Notably, PTX3 showed further positive associations with the PCT levels, and the hospital stay length. A plausible explanation of these findings could be that the elevated PTX3 levels are associated with inflammation and tissue damage, and the positive correlations with WBC and neutrophil counts as well as the ESR, CRP, and PCT support the role of PTX3 as a marker of inflammation in pediatric CAP. The positive correlation with hospital stays length suggests that higher PTX3 levels are associated with prolonged hospitalizations, reflecting the severity of illness and the extent of systemic inflammation and tissue damage in pediatric CAP.

Our study findings are in agreement with the study of Agrawal and colleagues [17] who found that PTX-3 was produced in response to proinflammatory stimuli. Contradictory results were presented in the study of Kim and colleagues [12] who found that the association of PTX3 levels with the inflammatory markers including WBCs count and ESR as well as the hospital stay length was statistically insignificant. This discrepancy may stem from differences in study populations, methodologies, or sample sizes.

In the present work, ROC analysis to identify diagnostic markers for CAP demonstrate that a CRP level of 5.24 mg/L, a PCT level of 0.51 ng/mL, and a PTX3 level of 7.94 ng/mL demonstrate strong discriminatory ability, with high specificity ensuring few false positives and sensitivity capturing a significant proportion of patients with CAP. However, comparison of the ROC curves related to the three markers highlighted the superior diagnostic performance of PTX3 in discriminating patients of CAP compared to CRP and PCT. This suggests that PTX3 is more effective than CRP and PCT in accurately identifying individuals with CAP, offering greater sensitivity and specificity.

This superior diagnostic performance was described in the study of Zhou and colleagues [13] who reported that ROC analysis showed that the area under the

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curve of PTX3 was largest in diagnosis of respiratory failure in pediatric patients with CAP.

Conclusion

Pentraxin-3 emerges as a promising biomarker for CAP diagnosis and severity assessment, exhibiting potential advantages over conventional markers like CRP and PCT. The findings highlight the clinical utility of PTX-3 in discriminating CAP patients from healthy controls with high sensitivity and specificity. Additionally, elevated PTX-3 levels were associated with respiratory distress and lung complications, indicating its potential role in identifying severe cases requiring intensive management. Such insights are valuable for optimizing clinical decision-making and improving outcomes in pediatric CAP.

However, further prospective studies are warranted to validate these findings and elucidate the precise role of PTX-3 in guiding therapeutic interventions and prognostication strategies for pediatric CAP.

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Author contribution

Authors contributed equally to the study.

Conflicts of interest

No conflicts of interest

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