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Original article

Serum S100A12 as a Marker of Severity in Children with Community Acquired Pneumonia

Background: *Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality among children. S100A12 is suggestive to be a useful marker for diagnosis and severity assessment of CAP. We sought to assess the serum level of S100A12 in children with complicated and noncomplicated CAP and its correlation to CAP severity and prognosis.* ***Methods:*** *In this controlled cross-sectional study, we measured serum levels of S100A12 using enzyme linked immunosorbent assay in 30 patients with complicated CAP, 30 patients with noncomplicated CAP and 30 healthy children. CAP severity was assessed using British Thoracic Society (BTS) criteria. Serum S100A12 levels, serum C- Reactive Protein (CRP), and serum procalcitonin (PCT) concentrations were quantified. Radiological assessment included chest x ray, lung ultrasound, and Computed Tomography (CT) scans.* ***Results:*** *Serum S100A12 levels were significantly higher in CAP patients (median 451.22 ng/mL) than in controls (median 112.65 ng/mL). Complicated CAP cases had higher S100A12 levels (587.92 ng/mL) than noncomplicated cases (330.11 ng/mL). A cutoff value of >410.23 ng/mL predicted complicated CAP with 83.33% sensitivity and 70.00% specificity. S100A12 levels were also significantly elevated in severe CAP cases.* ***Conclusions:*** *Serum S100A12 is a promising biomarker for CAP severity assessment. Higher levels are associated with complicated CAP and may help predict disease severity and prognosis in affected children.*

Keywords: Community-acquired pneumonia, S100 calcium-binding protein A12 (S100A12).

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INTRODUCTION

Community-acquired pneumonia (CAP) is a leading cause of illness and death among children.[1] Each year, CAP is responsible for the deaths of nearly one million children, accounting for 19% of all fatalities in those under the age of five. Most pneumonia-related deaths occur in developing countries. [2]

CAP has an annual incidence of 30 to 40 cases per 1,000 children under the age of 5 years and approximately 16 cases per 10000 children under 18 years who require hospitalization. In comparison to mild CAP, severe CAP can lead to serious complications and has a high mortality rate. [3]

Complicated CAP is a severe infection that includes various local and systemic complications. Recognizing severe and complicated forms of CAP is crucial for early hospitalization and appropriate treatment to minimize mortality. [4]

Several methods have been recognized for assessing the severity and complications of CAP in children. These include artificial intelligence-based analysis of computed tomography, evaluation of viral load using polymerase chain reaction, and the identification of specific clinical signs.[5] However, the high costs associated with these technologies and the advanced level of expertise they require present significant barriers to their widespread clinical use. [6]

There are limited pneumonia severity scores available for pediatric patients, such as those developed by the British Thoracic Society (BTS).[7] Additionally, there are few methods for predicting the severity of CAP in children. Although circulating biomarkers have limited sensitivity and

specificity, they are thought to be useful tools for predicting clinical prognosis in individuals with CAP. As a result, there is increasing interest in finding readily available circulating host biomarkers to enhance the evaluation of CAP risk and severity in children. [6]

S100A12 is a calcium-binding protein that belongs to the S100 family of low-molecular-weight proteins. Recently, serum S100A12 markers have been used for the differential diagnosis of clinical infectious diseases. However, data on the role of these biomarkers in the severity and complication prediction of childhood CAP is limited. [8]. A recent study indicated that S100A12 can be utilized to predict pneumonia severity in adults. However, its exact role in CAP in children is still unclear. Furthermore, little is known about the relationships between S100A12 levels and clinical characteristics, serum CRP concentrations, and serum procalcitonin concentrations. [9]

This study aimed to evaluate serum S100A12 levels in children with CAP and analyze its association with the severity and complications of CAP in children admitted to the Pediatric Pulmonology Unit at Ain Shams University Hospital.

METHODS

Study design

This was a controlled cross-sectional study conducted at the Pediatric Pulmonology Unit in the Pediatric Department of Ain Shams University. The study involved 90 children, including 30 with non-complicated CAP, 30 with complicated CAP, and 30 apparently healthy children matched for age and sex as controls.

The study has been approved by the Research Ethics Committee of the Faculty of Medicine at Ain Shams University [approval number MS457/2024]. This research complies with the ethical standards set by the institutional research committee and adheres to the principles of the 1964 Helsinki Declaration and its subsequent amendments. Informed written consent was obtained from the parents or caregivers of participants before enrollment.

Patients' selection

Inclusion criteria for this study were all children aged between 2 month and 12 years who had been diagnosed with CAP, as determined by the following [10]: a) The presence of signs and/or symptoms consistent with a lower respiratory tract infection, including fever (≥38°C), cough, tachypnea, retractions, and/or auscultation findings such as crackles, bronchial breathing, or diminished breath sounds, b) Radiological findings indicative of pneumonia. Complicated CAP included in this study comprised both local complications (such as parapneumonic effusion, empyema, and necrotizing pneumonia) and systemic complications (bacteremia, metastatic infection, multiorgan failure, acute respiratory distress syndrome, disseminated intravascular coagulation).[4]

Patients with chronic pulmonary disease, known cardiac, renal, hepatic, gastrointestinal, skin, hematologic, neuromuscular, immunodeficiency, and endocrinal diseases, as well as those patients hospitalized within 1 month before admission were excluded, to exclude possible hospital-acquired pneumonias.

Pneumonia severity grading was implemented according to the British Thoracic Society (BTS) guidelines for managing CAP in children. Patients were categorized into mild to moderate pneumonia and severe pneumonia groups based on various clinical criteria.[7] Parapneumonic pleural effusions were classified into Uncomplicated parapneumonic effusions, Complicated parapneumonic effusions and Empyema thoracis according to pleural fluid appearance, pH, LDH levels, glucose levels, Gram stain and culture results.[11] Parapneumonic effusions were categorized according to CT findings into *mild, moderate,* and *severe* based on the size of the effusion, anteroposterior (AP) quartile and maximum AP depth measured at the midclavicular line.[12]

All children received a comprehensive assessment of their medical history. This included demographic information such as age, sex, and residence, as well as details about any symptoms of respiratory illness or other systems. The assessment also covered the duration of illness, previous hospitalization history, antibiotics used prior to admission, vaccination history, anthropometric measurements, vital signs, and a local chest examination.

Radiology investigations:

Chest x-ray, and lung ultrasound, were done for all patients and Computed Tomography (CT) scans were performed in all complicated CAP patients and 6 patients with noncomplicated CAP to identify pneumonia signs and complications.

Laboratory investigations

Complete blood counts (CBC) were performed using the Sysmex XN-1000 (Sysmex Corporation, Japan). Serum concentrations of C-reactive protein (CRP) and procalcitonin (PCT) were measured using scattering turbidimetry with the Cobas analyzer system (Roche Diagnostics, Mannheim, Germany) and electrochemiluminescence with the

Cobas e411 analytical system (Roche Diagnostics, Mannheim, Germany), respectively. The serum levels of S100A12 were determined using a Human S100A12 ELISA Kit (Catalogue No. 201-12-4844, Shanghai Sun Red Biological Technology Company, Ltd., Shanghai, China). The sensitivity of the assay was 12.108 ng/ml, and the assay range was 13 ng/ml to 3200 ng/ml.

Microbiological Tests

Bacterial cultures were done for aerobic bacteria in sputum, pleural fluid and blood specimens. Sputum samples were collected by expectoration if the child was old enough to produce an adequate sample or in younger children who could not expectorate sputum, induced sputum was collected by postural drainage and thoracic percussion assisted by a respiratory therapist. Each specimen was cultured on Blood agar, Chocolate agar and MacConkey agar plates (Oxoid, UK) by semi-quantitative technique. Plates were incubated aerobically for 24-48 hours at 38°C. Positive bacterial cultures were identified by conventional microbiological techniques such as colony morphology, gram stain characteristics, and biochemical reactions and were tested for antimicrobial susceptibility. Additionally, 1-3 mL blood was directly inoculated aerobically into the blood culture bottle. Bottles were incubated at BacT/Alert automated Blood culture system at 36°C ±1°C for up to 5 days. Positively signaled blood culture bottles were subcultured on blood agar, MacConkey agar and Chocolate agar plates. Blood and MacConkey agar plates were incubated at 36°C ±1°C for 48 hours under aerobic conditions. Chocolate agar plates were incubated at 36°C ±1°C under aerobic conditions with an added 5_10% Co2. The growing colonies were identified by conventional microbiological methods (Gram stain, biological reaction, Colony morphology.

Sample Size

After reviewing previous study results,[9] we determined that a sample size of 30 patients diagnosed with uncomplicated CAP, 30 patients diagnosed with complicated CAP, and 30 healthy controls is sufficient to achieve 100% power at an alpha error of 0.05. This conclusion is based on the sample size calculation conducted using Power Analysis Sample Size (PASS 15), Version 15.5.10.

Statistical analysis

Statistical analysis was conducted using the latest certified version of SPSS software version 27. An Excel spreadsheet was created for data entry. Quantitative data with a normal distribution were presented as mean and standard deviation, whereas those with abnormal distribution were presented as median and interquartile range (IQR). Qualitative data were displayed as numbers and percentages. Mann-Whitney test was used to compare the median between the two groups, while the chi-square ($\chi 2$) test was utilized to compare qualitative variables.

Student's t-test was employed to compare the means of two independent groups. The Kruskal-Wallis test was applied to compare abnormally distributed quantitative variables across more than two groups. For normally distributed quantitative variables, we used the Analysis of Variance (ANOVA) F-test to compare multiple groups. Subsequently, we conducted pairwise comparisons using the Least Significant Difference (LSD) test as part of the Post Hoc analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values for specific parameters in predicting complicated CAP. Univariate and multivariate logistic regression analyses were used to predict complicated pneumonia. The level of significance was set at $p < 0.05$.

RESULTS

There were notable differences among the three groups when it came to CRP, procalcitonin, and S100A12 levels. The median S100A12 serum level was significantly higher in complicated CAP (587.92 ng/ ml) than control (112.65 ng/ ml) and in complicated CAP than noncomplicated CAP (330.11 ng/ ml) ($p <0.01$). (Table 1).

S100A12 serum levels were significantly higher in patients with severe pleural effusion than mild and moderate effusion ($P< 0.01$), and in patients with empyema than noncomplicated pleural effusion ($P < 0.01$). In patients with CAP categorized as mild to moderate severity according to the BTS guidelines, the median S100A12 level was 268.58 ng/ml which was significantly lower than the median level of S100A12 in patients classified with severe CAP, which was 489.8 ng/ml ($p < 0.01$). (Table 2).

This study showed significant positive correlation between S100A12 serum levels and total leukocyte count (cells/cmm), absolute neutrophilic count, CRP and length of hospital stay, p-value ($p<0.001$) (Table 3).

In the analysis of the ROC curve for predicting CAP, the best cutoff value for serum S100A12 was found to be greater than>198.86 ng/ml with sensitivity (95%), and specificity (96.7%), S100A12 is more sensitive (95.0%) than PCT (93.3%) but less than CRP (98.3%). All the three biomarkers showed high predictive power for

predicting pneumonia (AUC near 1) but S100A12 had lower specificity (96.7 %) than both CRP and procalcitonin (100%). (Table 4, Fig.1).

In the analysis of the ROC curve for predicting complicated CAP, the best cutoff value for serum S100A12 was found to be greater than 410.23 ng/ml. This cutoff demonstrates a sensitivity of 83.33% and a specificity of 70.0%. In contrast, the best cutoff value for serum CRP in predicting complicated CAP was determined to be more than 38 mg/L, which shows a sensitivity of 96.67% but a lower specificity of 46.67%, indicating a high false-positive rate. While S100A12 exhibits less sensitivity compared to CRP, it is more specific, making it a more reliable predictor of complicated CAP. Overall, S100A12 has superior diagnostic performance compared to CRP, as evidenced by a higher area under the curve (AUC) and better specificity, positioning it as a more balanced predictor (Table 5, Fig.2).

Logistic regression analysis and multivariate logistic regression analysis were utilized to predict complicated CAP. Both S100A12 levels exceeding 410.23 ng/mL and CRP levels exceeding 38 mg/L were found to be statistically significant predictors of complicated CAP in both univariate and multivariate models ($p < 0.05$). S100A12 demonstrated a high odds ratio (OR) of 11.667 in the univariate model and 14.251 in the multivariate model, confirming its independent association with complicated CAP. Furthermore, CRP exhibited an even higher OR of 25.375 in the univariate model and 36.350 in the multivariate model, indicating that patients with CRP levels greater than 38 mg/L are significantly more likely to develop complicated CAP (Table 6).

Table 1. Comparison between control, non-complicated CAP and complicated CAP groups regarding serum S100A12, CRP, and procalcitonin

		Control group	**Non - Complicated group**	**Complicated group**	**Test value**	**P-value**
		No.= 30	**No.= 30**	**No.= 30**		
CRP (mg/L)	Median (IQR)	2 (2 - 3)	54 (15 - 87)	83.5 (65 - 117)	61.064≠	0.000
	Range	1 – 8	2.2 – 369	32 – 443		
Procalcitonin (µg/L)	Mean ± SD	0.05 ± 0.01	1.64 ± 3.43	1.77 ± 0.7	6.739•	0.002
	Range	0.03 – 0.07	0.06 – 18	0.25 – 3.1		
S100A12 (ng/ ml)	Median (IQR)	112.65 (105.31 - 147.95)	330.11 (217.8 - 489.78)	587.92 (448.9 - 806.19)	60.579≠	0.000
	Range	55.45 – 227.27	103.1 – 1073.1	207.52 – 1409.4		
Post Hoc analysis by LSD and multi-comparison between groups						
Parameters		**Control group Vs Non - Complicated group**	**Control group Vs Complicated group**	**Non - Complicated group Vs Complicated group**		
CRP (mg/L)		0.000	0.000	0.009		
Procalcitonin (µg/L)		0.003	0.001	0.803		
S100A12 (ng/ ml)		0.000	0.000	0.000		

•: One Way ANOVA test; ≠: Kruskal-Wallis test

Table 2. Relation between S100A12 serum level with pneumonia severity, and pleural effusion characteristics

		S100A12 (ng/ ml)		**Test value**	**P-value**
		Median (IQR)	**Range**		
BTS guidelines assessment	Mild to moderate	268.58 (138.5 – 332.57)	123.85 – 438.5	2.661	0.008
	Severe	489.8 (332.57 – 739.6)	103.1 – 1409.4		
Amount of pleural effusion	Mild	404.12(371.68 –453.54)	207.52 – 752.77	18.789	0.000
	Moderate	600.5(560.26 – 739.6)	448.9 – 1157.9		
	Severe	873.85 (818.45 1017.5)	806.19 – 1409.4		
Type of pleural effusion	Non-complicated	393.11 (311.95 –453.54)	207.52 – 553.7	16.867	0.000
	Complicated	587.92 (471.24 – 739.6)	371.68 – 872.43		
	Empyema	818.45 (752.77 – 1017.5)	560.26 – 1409.4		

Table 3. Correlation between S100A12 and some studied parameters in pneumonia patients

	S100A12 (ng/ ml)	
	r	**p-value**
Total leukocyte count (cells/cmm)	0.666**	0.000
Absolute neutrophilic count (cells/cmm)	0.732**	0.000
Lymphocyte (cells/cmm)	0.129	0.327
Platelet (thousands/cmm)	0.514**	0.000
CRP (mg/L)	0.868**	0.000
Procalcitonin (µg/L)	0.897**	0.000
Length of hospital stay (days)	0.477**	0.000

Spearman correlation coefficient.

Table 4. Diagnostic Performance of CRP, Procalcitonin and S100A12 in Predicting pneumonia

	Cut off point	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
CRP (mg/L)	>8	0.992	98.3	100.0	100.0	96.8
Procalcitonin (µg/L)	>0.07	0.987	93.3	100.0	100.0	88.2
S100A12 (ng/ml)	>198.86	0.973	95.0	96.7	98.3	90.6

AUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value

Table 5. Diagnostic Performance of CRP and S100A12 in Predicting Complicated CAP

	Cut off point	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
CRP (mg/L)	>38	0.697	96.67	46.67	64.4	93.3
S100A12 (ng/ml)	>410.23	0.782	83.33	70.00	73.5	80.8

AUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value

Table 6. Univariate Logistic Regression Analysis and Multivariate Logistic Regression Analysis for association of CRP and S100A12 with complicated CAP

	Univariate				Multivariate (Backward model)			
	P-value	OR	95% CI		P-value	OR	95% CI	
			Lower	Upper			Lower	Upper
CRP >38 mg/L	0.003	25.375	3.050	211.104	0.021	36.350	1.704	775.207
S100A12 >410.23 ng/mL	0.000	11.667	3.384	40.220	0.023	14.251	1.438	141.237

OR: Odds ratio; CI: Confidence interval

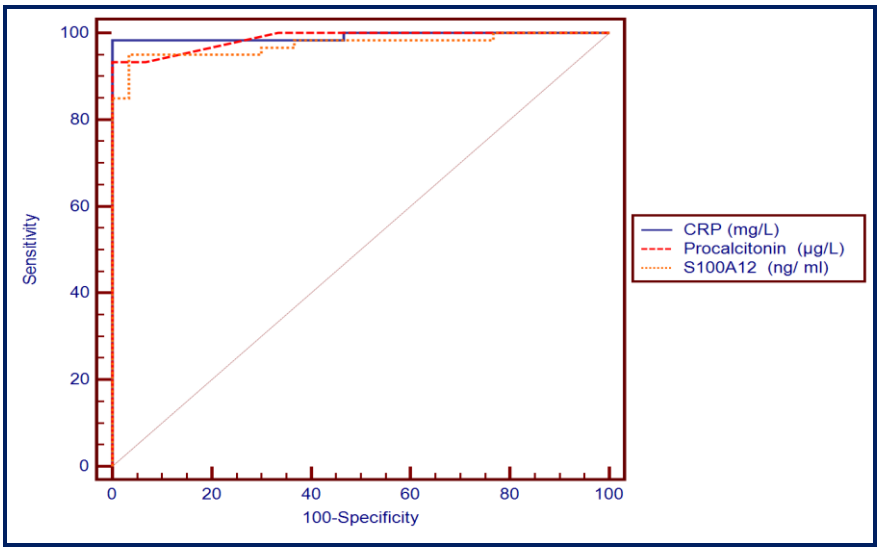

Figure 1. Receiver operating characteristic (ROC) curve for CRP, procalcitonin and S100A12 levels as a diagnostic marker to differentiate between control and pneumonia group

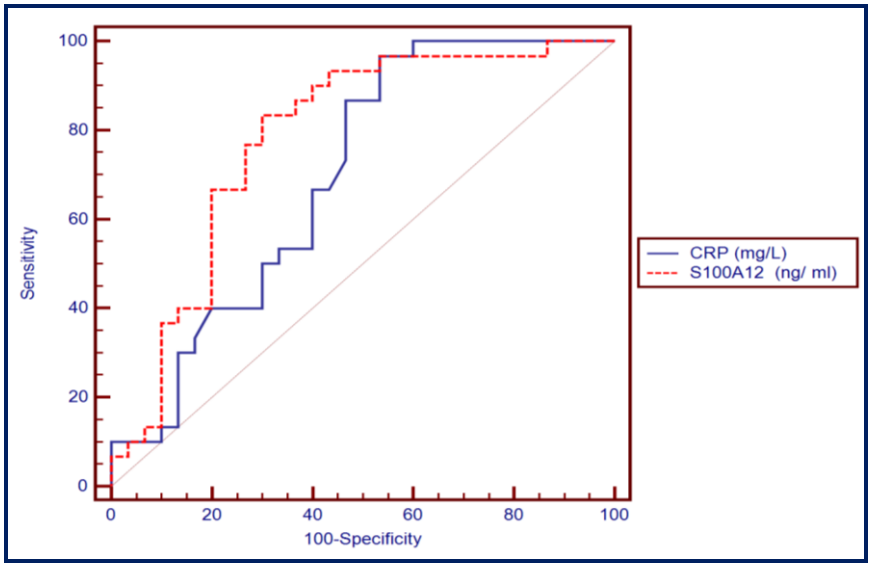

Figure 2 Receiver operating characteristic (ROC) curve for CRP and S100A12 levels for differentiation between non complicated CAP and complicated CAP groups

DISCUSSION

Most of the studies investigating S100A12 serum levels in CAP were done in adults. Our study revealed that serum S100A12 was significantly higher in children with CAP (median 451.22 ng/ ml) than control (112.65 ng/ ml). This finding aligns with previous research showing that serum S100A12 was increased in adult CAP patients compared to control subjects [13]. Also, Wang et al., (2023) found that serum S100A12 concentrations in adult patients with CAP were higher than those in healthy controls. They attributed the increase in S100A12 to the release of excessive inflammatory factors, which caused an excessive inflammatory response and aggravated tissue damage.[9] Jiang et al., (2021) suggested that the life span of neutrophils is very short, and the death and necrosis of neutrophils also induce the elevation of S100A12 in human bodies.[14] Cronkite et al., (2018) suggested that the infection of streptococcus pneumoniae, or other pathogenic bacteria, activated the immune system and evoked the elevation of neutrophils and production of S100A12 in human bodies which further activates inflammatory signaling pathways and causes secretion of inflammatory cytokines. In turn, inflammatory cytokine secretion persistently induces the elevation of S100A12 in CAP patients.[15]

This study showed that S100A12 serum level was significantly higher in complicated CAP

(587.92 ng/ ml) than noncomplicated CAP (330.11 ng/ ml) with p value <0.01. The median S100A12 in non-severe CAP patients assessed according to BTS guidelines was 268.58 ng/ ml which was significantly lower than the median level in severe CAP patients (489.8 ng/ ml) (p <0.01). This result was in consistence with Jiang et al,[14] who found that the level of serum S100A12 correlated positively with clinical severity scores in CAP patients and elevated serum S100A12 on admission increased the risk of death and hospital stay in adult CAP patients during hospitalization. They postulated that under physiological conditions, there is sufficient storage of S100A12 in neutrophils and myeloid cells, and S100A12 is significantly elevated during infection, and many other inflammatory diseases. Zhou et al., (2024) showed that serum S100A12 can effectively predict the mortality risk in adult CAP patients after 30 days and serum S100A12 combined with clinical assessment score has a high clinical application value in evaluating the severity and prognosis of adult CAP. [15]

This study showed significant positive correlation between S100A12 and total leukocyte count, absolute neutrophilic count, CRP and length of hospital stay, with p-value (p<0.001). This agreed with Wang et al., (2023) who found that in adult patients with CAP, there was positive correlation between serum S100A12 concentrations with serum CRP, PCT concentrations, length of hospital stay and pneumonia severity. They suggested that serum S100A12 concentrations may play an important role in the progression of disease and the inflammatory response in the body. Additionally, S100A12 concentrations may complement CRP and PCT concentrations for evaluating the inflammatory response and severity of CAP, and thus more accurately predicting severity [9]. Similarly, Jiang et al, showed that S100A12 was positively associated with the counts of white blood cell, neutrophil, procalcitonin, and C-reactive protein .[14]

The best cut off value of serum S100A12 for prediction of complicated CAP in our study was >410.23 ng/ ml with sensitivity 83.33% and specificity 70.00%. S100A12 demonstrated a high odds ratio (OR) in the univariate model and in the multivariate model, confirming its independent association with complicated CAP. Zhou et al., (2024) in adult patients showed that best cut off value of serum S100A12 for predicting CAP deaths was >18.190 ng/ ml with sensitivity 85.7 % and specificity 72.4%. They showed that in Multivariate logistic regression analysis S100A12 was independent risk factors for predicting 30-day mortality in adult CAP patients. They postulated that S100A12 can be used in adult patients to assess the severity and evaluate the prognosis of CAP. [13]

In conclusion, serum S100A12 might serve as a valuable add-on laboratory test for diagnosing CAP and predicting severe cases. Elevated levels of S100A12 are positively correlated with complications, longer hospital stays and severity of CAP in these patients. The limitations of this study include several factors. First, it was a single-center study with a relatively small sample size. To strengthen our findings, future research should involve multicenter studies with larger sample sizes. Second, the level of S100A12 was only measured in serum; it would be beneficial to evaluate S100A12 in the bronchoalveolar lavage fluid of patients with CAP in future studies. Lastly, our study did not compare the diagnostic effectiveness of S100A12 with other indicators such as interleukin 6 (IL-6), serum amyloid A, ferritin, neutrophil CD64, and heparin-binding protein (HBP), all of which also reflect the severity of the infection.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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