Procalcitonin, C-reactive Protein and White Blood Cells Count in Children With Community Acquired Pneumonia

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Abstract:

Background: community-acquired pneumonia (CAP) is one of the most common pediatric diseases. Early and accurate diagnosis of CAP in children has a great value in avoiding pneumonia complications and decreasing rates of pneumonia related mortality. **Aim of the work:** this study aimed to investigate the role of procalcitonin (PCT), C-reactive protein (CRP) and white blood cells (WBCs) count in diagnosis of childhood CAP. **Patients and Methods:** 90 infants and children aged from 2 months to 5 years (60 months) were included in this study. They were divided into two groups group I: 60 patients hospitalized for CAP and group II: 30, age and sex matched, healthy controls attending the outpatient clinics of the same hospitals for routine care. Chest x-ray was performed to the patients group only, while WBCs count, serum CRP, serum procalcitonin were applied to both patients and controls. **Results:** WBCs count, neutrophil percentage, CRP level, procalcitonin concentration were higher in the patients group than the controls with high statistically significant difference (13.4±3.4 vs 8.3±1.7) (54.5±15.4 vs 37.2±6.7) (57.5±30.1 vs 5.7±5.6) (0.5±0.47 vs 0.07±0.04) respectively. Using the AUROC test WBCs count at cut-off value >10.5 x10^3 cell/mm^3, CRP at cut-off value >20 mg/L, procalcitonin at cut-off value >0.17 ng/ml could predict presence of CAP in the patients with 83.3%, 85%, 86.7% sensitivity and 76.6%, 100%, 96.7% specificity respectively. **Conclusion:** evaluation of WBCs count, serum CRP and serum procalcitonin concentration has an important role in diagnosis of CAP in infants and children.

Keywords: CAP, WBCs, CRP, procalcitonin.

Abbreviations: AUC area under Roc curve, CAP community-acquired pneumonia, CBC complete blood count, CRP C-reactive protein, PCT procalcitonin, WBC white blood cell.

Introduction

CAP is one of the most common pediatric diseases. It is a major cause of respiratory morbidity and mortality in children worldwide. It is considered to be the leading cause of death in children younger than five years especially in the developing countries. [1] It is acute infection of the pulmonary parenchyma acquired in community in previously healthy children without predisposing factors. [2] Early and accurate diagnosis of CAP in children is critical to effective management to avoid complications of pneumonia and decrease rates of pneumonia related mortality.[3] Diagnosis of CAP is suggested by clinical features, such as fever and respiratory symptoms, however clinical presentation of pneumonia in children varies depending on the causative agent, the host age and the severity of infection. No single symptom or sign is specific for pneumonia. [4]

Plain chest radiography is considered gold standard for confirming the diagnosis of pneumonia when it is clinically suspected, but there are a lot of limitations for using chest radiography in children and it is not recommended to be performed routinely.[5] Etiological diagnosis of pneumonia through microbiological methods is not always accessible in infants and young children as there is limited possibility of obtainingadequate respiratory specimens.[6]

WBCs count has long been used by clinicians to help in diagnosis of pneumonia, determining its severity and predicting patient outcome.[7] Generally, patients with bacterial pneumonia have WBCs count more than 15,000/mm^3, however in 5–10% of cases WBCs count can be lower than 6,000/mm^3.[8]

There are several inflammatory biomarkers that increase in the body in response to infection. These biomarkers could be useful in predicting pulmonary involvement and stratifying children who should do further radiographic investigation.[9]

CRP is an inflammatory biomarker synthesized by the liver in response to inflammation. It is mainly used as a diagnostic tool of acute infection in febrile children. Its level is significantly higher in bacterial compared to viral infection.[10] Procalcitonin is another inflammatory biomarker increases in response to inflammation, especially that caused by bacterial infection. It does not

significantly rise with viral or non-infectious inflammations.[11]

These biomarkers have been studied and used in adult clinical practice and have provided further improvements toward solving CAP diagnostic and therapeutic problems. Unfortunately, only few studies have examined the roles of these biomarkers in pediatric practice.[12]

Aim of the work:

The aim of this study is to investigate the role of procalcitonin, CRP and WBCs count in diagnosis of childhood community acquired pneumonia.

Patients and Methods

This case-control study was conducted in pediatric departments of Benha and Kafr El Sheikh University Hospitals during the period from June 2019 to January 2020. The study comprised 90 infants and children aged from 2 months to 5 years (60 months). They were divided into 2 groups:

- **Group I (patients group):** comprised 60 patients hospitalized for CAP. They were 38 males and 22 females. Their age ranged from 2 months to 5 years (60 months).
- **Group II (control group):** comprised 30, age and sex matched, healthy controls attending the outpatient clinics of the same hospitals for routine care. They were 19 males and 11 females. Their age ranged from 6 months to 5 years (60 months).

The study was approved by the ethical committee of Faculty of Medicine, Benha University. Informed consents were obtained from all participants.

Inclusion criteria: Patients aged from 2 months to 5 years hospitalized with diagnosis of CAP according to the WHO (2019) criteria namely cough and/or difficult breathing with or without fever in addition to presence of fast breathing or lower chest wall in-drawing. Diagnosis was confirmed by the presence of bronchial breathing, bronchophony and crackle on chest auscultation as well as consolidation in chest X-ray.

Exclusion criteria: Patients with hospital acquired infection (patients with a prior hospitalization within 2 weeks of a current diagnosis of pneumonia), patients with congenital chest malformations, patients with clinically detected infections in other parts of the body, patients who started antibiotic treatment before hospital admission, patients with other diseases as congenital heart disease, tuberculosis, diabetes, hepatitis, liver cell failure etc, immuno-compromised patients, children whose patients did not

give informed consent were excluded from the study.

All participants in the study were subjected to the following:

1. Full history taking: with stress on age, dietetic history, history of symptoms of pneumonia e.g. cough, fever, difficult breathing, grunting and refusal of feeding, past history of similar illness or chest diseases and history of presence of other infection in the body.

2. Thorough clinical examination including: general examination including oxygen saturation by pulse oximeter and local chest examination with focus on inspection and palpation of chest movements and auscultation of air entry and breath sounds.

3. Chest radiography: postero-anterior views (for the case group only).

4. Laboratory investigations including:

• **Complete blood count (CBC):** including WBCs count with manually verified differential count including neutrophil and lymphocyte. In the pediatric population, leukocytosis is usually defined as a WBC count > 15,000 cells/mm^3.[8] The CBC also involved hemoglobin concentration, RBCs count and platelet count . Two ml sample of peripheral blood was withdrawn from subjects to potassium EDTA tube and analyzed using cell counter: ABX Pentra XL 80 (Horiba, France).

• **CRP:** Two ml sample was withdrawn from subjects to plain tube (without additives) then left in room temperature for 15 minutes for clotting. Sample was then centrifuged for 10 minutes at 4000 round/min and serum was then separated. Ten µl of serum was analyzed for CRP using commercial kits (Biosystem) by turbidimetric method on spectrophotometer (ERMA, Japan). According to the manufacturer's instructions, the limit of quantitation was 0.5 mg/L and the upper limit of normal was 6 mg/L.[13]

• **Procalcitonin:** From the same serum sample of CRP, 50 µl of serum was obtained for PCT analysis. Analysis was done by commercial kits (NOVA ELISA kits) using sandwich-ELISA method. According to the manufacturer's instructions, the detection limit was 0.01 ng/ml and the suggested upper limit for normal PCT was 0.1 ng/ml.[14]

Principle of Procalcitonin test: (Sandwich principle): 1^{st} incubation: antigen in the sample (30 µL), a biotinylated monoclonal PCT-specific antibody, and monoclonal PCT-specific antibody labeled with a ruthenium complex[a] react to form a

sandwich complex.2nd incubation: after addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode. Total duration assay was 18 minutes.

Statistical Analysis: The data was analyzed using SPSS 24 Inc. Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. The qualitative data represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact wereused to calculate difference between qualitative variables as indicated. The quantitative data were expressed as median and range for being non-parametric data (not normally distributed). Mann-Whitney test were used to calculate difference between quantitative variables in two groups for non-parametric variables. Spearman's correlation tests were used for correlating non-parametric variables.

Results:

Table (1) shows that WBCs count, neutrophil percentage, serum CRP level and serum PCT concentration were higher in the patients group compared to the control group with high statistically significant differences. Figure (1) shows that there was significant positive correlation between serum PCT and body temperature. Figure (2) shows that there was significant positive correlation between serum PCT and WBCs count. Figure (3) shows that there was significant positive correlation between serum PCT and serum CRP. Table (2) shows that WBCs count at cut-off value $>10.5x10^3$cells/mm^3could predict presence of CAP in the patients group with 83.3% sensitivity and 76.6% specificity. Table (3) shows that CRP at cut-off value >20 mg/L could predict presence of CAP in the patients group with 85%sensitivity and 100% specificity. Table (4) shows that serum PCT at cut-off value >0.17 ng/ml couldpredict presence of CAP in the patients group with 86.7% sensitivity and 96.7% specificity.

Table (1): Laboratory investigation findings in the studied groups

CBC findings	Group				MW Test	P-value Sig.
	Patients		Control			
	Mean±SD	Median (range)	Mean±SD	Median (range)		
WBCs, ($x10^3$/µL)	13.4 ± 3.4	13 (8-26.2)	8.3 ± 1.7	8.5 (4.9-11)	- 6.8	**<0.001 HS**
Neutrophils (%)	54.5 ± 15.4	57.5 (20-85.4)	37.2 ± 6.7	38.2 (23.7-48.6)	-4.9	**<0.001 HS**
Lymphocytes (%)	45.5 ± 15.1	37.5(15-77)	41± 5.6	44.1(34.7-55)	-1.9	0.236 NS
Hb (gm/dl)	11.4 ± 0.7	11.5 (10.5-12.8)	11.5 ± 0.8	11.5 (10.8-13)	-0.5	0.636 NS
RBCs ($x10^6$/µL)	4.2 ± 0.3	4.2 (3.7-4.8)	4.2 ± 0.4	4.1 (3.5-5)	-1.2	0.245 NS
PLT ($x10^3$/µL)	379.3±63.6	300 (180-455)	325.4 ± 78.3	296.5 (167-398)	-0.4	0.162 NS
CRP values (mg/L)	57.5 ± 30.1	68 (2-110)	5.6 ± 5.7	3.5 (1-20)	-6.9	**<0.001 HS**
Procalcitonin (ng/ml)	0.5 ± 0.47	0.38 (0.04-2.3)	0.07 ± 0.04	0.06 (0.02-0.2)	-6.9	**<0.001 HS**

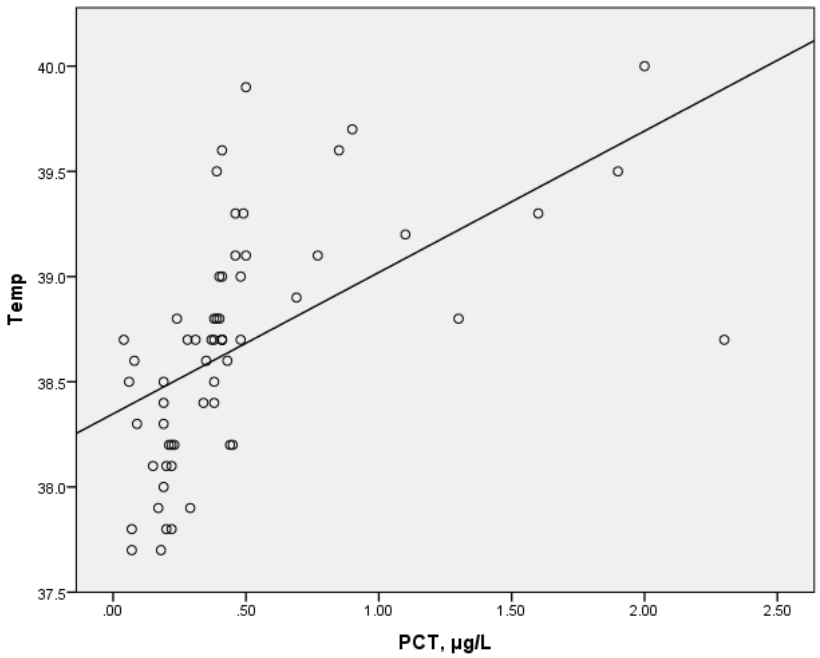

Fig (1): linear correlation between serum PCT and body temperature in the patients group

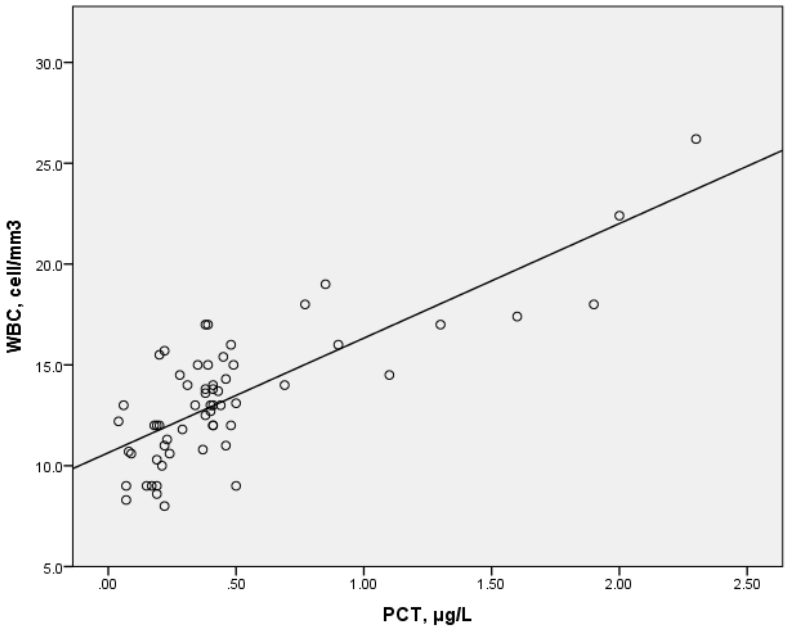

Fig (2): linear correlation between serum PCT and WBCs count in the patients group

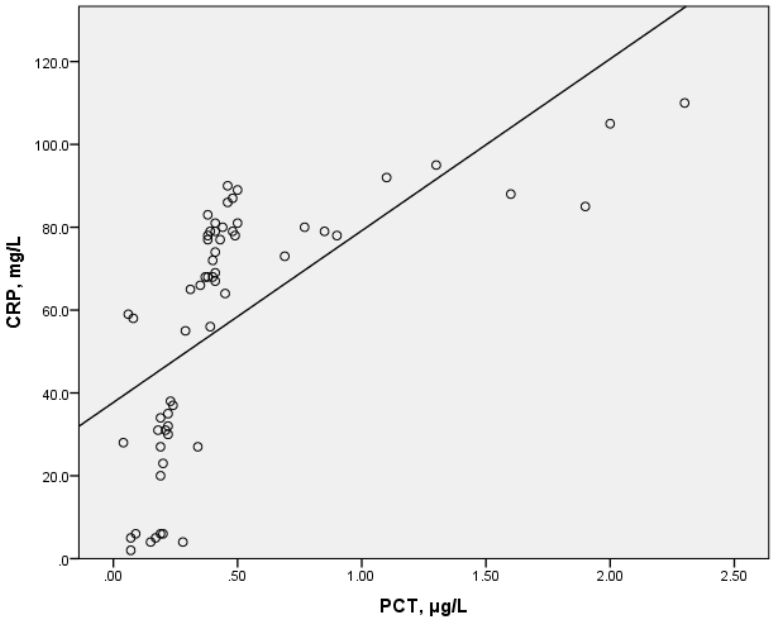

Fig (3): linear correlation between serum PCT and serum CRP level in the patients group

Table (2): Validity of WBCs count in predicting diagnosis of CAP in the patients group

Predictor	**WBCs count**
Cut-off	>10.5 x10^3 cell/mm^3
Sensitivity	83.3%
(95% CI)	(71.5% - 91.7%)
Specificity	76.6 %
(95% CI)	(61.5%-84.5%)
PPV	87 %
(95% CI)	(78%-91%)
NPV	69.6%
(95% CI)	(57%-79%)
AREA UNDER THE ROC CURVE (AUC)	0.821
Standard Error	0.02
(95% CI)	0.867 - 0.978
z statistic	19.313
P	**<0.001**

Table (3): Validity of serum CRP in predicting diagnosis of CAP in the patients group

Predictor	**CRP**
Cut-off	>20 mg/L
Sensitivity	%85
(CI %95)	(73.4% - 92.9%)
Specificity	% 100
(CI %95)	(88.4% - 100%)
PPV	100%
(CI %95)	
NPV	%77
(CI %95)	(64.6% - 85.9%)
AREA UNDER THE ROC CURVE (AUC)	0.951
Standard Error	0.02
(CI %95)	0.883 - 0.985
z statistic	21.723
P value	**0.001>**

Table (4): Validity of serum procalcitonin in predicting diagnosis of CAP in the patients group

Predictor	**PCT**
Cut-off	>0.17 ng/ml
Sensitivity	86.7%
(95% CI)	(75.4% - 94.1%)
Specificity	96.7%
(95% CI)	(82.8% - 99.9%)
PPV	98%
(95% CI)	(88.3% - 99.7%)
NPV	78%
(95% CI)	(65.5% - 87.4%)
AREA UNDER THE ROC CURVE (AUC)	0.952
Standard Error	0.02
(95% CI)	0.885 - 0.986
z statistic	21.972
P value	**<0.001**

Discussion:

This case control study was designed to assess the role of procalcitonin, CRP and WBCs count in diagnosis of childhood CAP. In the present study, we found thatWBCs count and neutrophil percentage were significantly higher in the patients group compared to the control group. This comes in agreement of the results ofprevious studies of Lee et al.,[15], Karadag-Oncel et al.,[16] and Sahin et al.,[17]. Elevated WBCs count and neutrophil percentage are considered to be a sign of inflammatory response caused by infection.[18] Serum CRP level in the patients group was significantly higher than that in the healthy controls. This comes in agreement with the results of Lee et al.,[15], Tatar et al.,[19] and Berg et al.,[20]. This comes in consistence with the role of CRP as an inflammatory biomarker closely related to the inflammatory reaction and tissue injury.[21]Procalcitonin level in our patients group was significantly higher than that in the healthy controls. This comes in agreement with the results of Lee et al.,[15] and Zhu et al.,[22]. This is a demonstration of the role of PCT as an acute phase reactant that increases in response to inflammatory processes.[23] Correlation analysis showed that there was a significant positive correlation between

serum procalcitonin level and body temperature. This comes in agreement with the results of previous study ofKorppi et al.,[24]. In contrast to that, Agnello et al.,[9] did not find any correlation between PCT and any of the patients' clinical finding. Procalcitonin, as an acute phase reactant increases in infection which is usually accompanied by elevated body temperature.[25] We also found significant positive correlations between serum procalcitonin level and both the CRP level and WBCs count. This agrees with the results of the previous studies of Don et al.,[26], Lee et al.,[15] and Agnello et al.,[9]. This finding can be explained by the fact that PCT is an acute phase reactant that increases in infection which is usually accompanied by leukocytosis and elevation of CRP.[25]The ROC curve analysis revealed that the WBCs count at the cutoff point of >10.5 $x10^3$ cell/mm^3 could predict the diagnosis of CAP in our patients group, with 83.3% sensitivity and 76.6% specificity. In the previous study ofBerg et al.,[20], it was found that the WBCs count at the cutoff value 12.2 x 10^3 cell/mm^3 could predict the diagnosis of CAP with 46% sensitivity and 80%specificity. The higher sensitivity and lower specificity in our study could be attributed to the low cut off value. Our study showed that the optimum diagnostic cutoff value of CRP for predicting the diagnosis of CAP was >20 mg/L with 85% sensitivity and 100% specificity. In the study of Lee et al.,[15], the optimum diagnostic cutoff point of CRP level was 6 mg/L with 90% sensitivity and 38% specificity. The big difference between the two studies regarding the specificity may be due to the large difference in the cutoff values between them. In this study, the optimum cutoff value of serum PCT for diagnosing CAP, according to the ROC curve analysis, was >0.17 ng/ml with 86.7% sensitivity and 96.7% specificity. According to the study of Lee et al.,[15], the sensitivity and specificity of serum PCT, at the cutoff value 1 ng/ml, were 90% and 83% respectively. The difference in the cutoff values of PCT for diagnosing CAP between the two studies could be explained by the difference in the upper limits of normal considered in each study. In our study it was 0.1 ng/ml, while in the study of Lee et al.,[15] it was 0.5 ng/ml.

In conclusion: evaluation of WBCs serum PCT concentration, serum CRP level has an important role in diagnosis of CAP in children.

Conflict of interest: There were no conflicts of interests and no funding during the study.

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