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Role of Procalcitonin as a Predictor of Complicated Acute Appendicitis

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Abstract

Background: Many complications arise as a result of delayed diagnosis and treatment of complicated acute appendicitis (CAA). C-reactive protein (CRP), white blood cell (WBC) count and procalcitonin (PCT) are among of the biochemical indicators that are utilized to improve the clinical prediction of acute appendicitis (AA).

Aim of Study: The aim of this study is to assess how useful serum PCT as a predictor for complicated acute appendicitis diagnosis, in order to help doctors make better decisions.

Patients and Methods: A total of 100 individuals who underwent open appendectomy from December 2017 to March 2021 in Tanta University Hospital, were included in this prospective cohort research. Upon admission, each patient had CRP, serum PCT, and Alvarado score assessment.

Results: There was a positive relationship between serum PCT and CRP (r=0.279, p=0.048). The optimum cutoff value was 1.07ng/ml, 30mg/l. PCT had a sensitivity of 85.71% and a specificity of 81.4%. For identifying patients with CAA using binary logistic regression analysis with CRP and PCT as independent variables. PCT elevation remained an independent marker for CAA after controlling for relevant confounding variables.

Conclusion: PCT levels can be assessed as a predictor in patients with complicated acute appendicitis which is strongly indicated in patients with PCT levels greater than 0.5ng/ml.

Key Words: *Complicated acute appendicitis – Appendectomy – Procalcitonin – CRP.*

Introduction

ACUTE Appendicitis (AA) is the most often encountered cause of acute abdominal pain in people of all ages **[1]**. 7-10% of the general population are suffering from AA, with the highest incidence in the second and third decades of life **[2]**. The most prevalent method to identify AA is still clinical examination, despite the fact that it can be mistaken with a number of other abdominal diseases. As a result, excluding such diseases solely on the basis of a clinical examination is challenging **[3]**.

The recognized gold standard for treating AA is open appendectomy (OA) for more than a century **[4]**. The current recommendation is inoperative care for uncomplicated appendicitis. As a result, operations should be avoided due to the danger of ileus (which happens in 1.2 percent of cases) and abdominal hernias (0.68 percent of cases) **[5]**.

Acute peritonitis can develop from CAA, such as perforated and gangrenous appendicitis, necessitating immediate surgery. CAA has been identified in 20% to 30% of the cases of appendicitis **[6]**.

The negative appendectomy rate (NAR) has been estimated to be between 9% and 44%, despite the use of laboratory testing, imaging methods, and numerous grading systems to validate the prediction of CAA **[7]**.

As a result of the high NAR, new prediction approaches with great sensitivity and specificity are being developed. Many inflammatory indications are utilized to predict acute abdominal disorders such CAA, such as (CRP) and an elevated total leukocyte count (TLC) **[8]**.

Procalcitonin (PCT) is an acknowledged lab marker for illness severity in infection and sepsis patients **[9]**. When it comes to bacterial infections, PCT levels rise more quickly, but when it comes to viral infections, they stay normal **[10]**.

Inflammation has been connected to the amount of PCT in the body. It is a more accurate predictor than C-reactive protein, which rises in inflammatory situations as well **[11]**. PCT can aid in the diagnosis of AA and the avoidance of unnecessary appendectomies **[12]**.

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Patients and Methods

After being diagnosed with AA, 100 patients of both sexes, ranging in age from 18 to 65 years, underwent open appendectomy. All of the patients had nausea, anorexia, vomiting, shifting soreness and tenderness in the right bottom quadrant, and/or other gastrointestinal symptoms. The diagnosis of AA was confirmed after auxiliary tests and post-operative pathology.

Pregnant women, patients with diagnoses other than AA, patients under the age of 18, patients with other infectious lesions, were all excluded.

Each patient who volunteered to take part in the trial signed a consent form. The research was approved by Tanta University's Ethical Committee.

The following data about each patient were collected:

The Alvarado score is based on the patient's history, subjective symptoms, physical findings in the abdomen, and the Alvarado score **[13]** (Table 1). The admissions process includes vital signs, laboratory tests (CBC, CRP, and PCT), and ultrasound.

PCT level was measured via an automatic analyzer, the VIDAS B.R.A.H.M.S PCT assay (BioMerieux, Marcy L'Etoile France).

Patients were categorized as having uncomplicated acute appendicitis (UAA) or complicated acute appendicitis (CAA) based on the pathology report (CAA).

Table (1): Alvarado score.

Alvarado score	N	%
2	1	2.0
3	1	2.0
5	11	22.0
6	18	36.0
7	12	24.0
8	3	6.0
9	3	6.0
10	1	2.0

The primary outcome was the predictive ability of procalcitonin for complicated acute appendicitis. The secondary outcome was the predictive ability of CRP for complicated acute appendicitis.

Sample size calculation:

The sample size calculation was performed using MedCalc V.20 (MedCalc Software Ltd). The sample size was calculated based on the following considerations: 0.05 α error, 95% power of the study, the prevalence of CAA was 60% with an AUC of 0.718 for PCT to predict development of complicated acute appendicitis (our primary outcome) according to a previous study **[14]** and 16 cases were added to overcome dropout.

Statistical analysis:

For statistical analysis, IBM© SPSS v25 (Chicago, IL, USA) was utilized. To assess the normality of the data distribution, the Shapiro-Wilks test and histograms were utilised. To analyse quantitative parametric data provided as mean and standard deviation, the unpaired student *t*-test was utilised (SD). The Mann Whitney-test was developed to examine non-parametric quantitative data presented as median and range. To analyse qualitative variables that were presented as frequency and percentage, the Chi-square test or Fisher's exact test was used (%). Spearman correlation was used to determine the degree of correlation between two variables. The overall diagnostic performance of each test was assessed using ROC curve analysis. Using logistic regression analysis, the independent predictors of complex appendicitis were identified. Statistical significance was determined using a two-tailed p-value <0.05.

Results

A total of 14 instances of uncomplicated acute appendicitis (UAA) were documented, while 86 cases of severe acute appendicitis were reported (CAA).

A statistically difference was not found between CAA and UAA in terms of age, gender, WBC, neutrophils, PDW: Platelet distribution width, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red cell distribution width, platelets, and MPV: Mean platelet ($p>0.05$). Furthermore, the CRP and PCT levels in the CAA group were considerably higher than in the UAA group ($p=0.003$ and 0.021, respectively). (Table 2).

Correlation between PCT and other markers:

Serum PCT was found to be positively correlated with CRP in a Spearman correlation analysis ($p=0.048$, $r=0.279$), while there was no significant relationship between PCT and other metrics, there was a strong link between PCT and other factors. (Table 3).

Receiver operating characteristic (ROC) analysis of PCT and other factors for diagnosing CAA:

Receiver operating characteristic (ROC) analysis was used to further evaluate the diagnostic

value of CAA. PCT (0.841, 95% CI 0.709-0.929) >CRP (0.771, 95% CI 0.630-0.878) were the outcomes of the factors' area under curve (AUC) (0.841, 95% CI 0.709-0.929) (Fig. 1). Accordingly, the optimal cutoff value is 1.07ng/ml (30mg/l). PCT had a sensitivity and specificity of 85.71% and 81.4% for predicting CAA patients, respectively, while CRP had a sensitivity and specificity of 85.71% and 74.42%.

Logistic regression analysis of PCT and other factors:

PCT and CRP were employed as independent variables in a binary logistic regression study. PCT elevation remained an independent marker for CAA after accounting for all relevant confounding variables (p=0.019) (Table 4).

Table (2): Demographic and laboratory characteristics of the study group.

	UAA group (n=86)		CAA group (n=14)		*p*-value
	N	%	N	%	
Age (years)	6.44±1.76		5.86±1.21		0.476
Gender:					
Male	54	62.8	4	28.6	0.089
Female	32	37.2	10	71.4	
WBC (10^6/µL):					
Mean ± SD	011537.40± 3712.77		14584.14± 3770.34		0.056
Neutrophils (%):					
Mean ± SD	72.58±11.29		75.71±6.24		0.546
CRP:					
Mean ± SD	27.47±4.53		39.71±24.38		0.021
PDW:					
Mean ± SD	14.93±2.13		15.71±1.60		0.364
NLR:					
Mean ± SD	5.77±1.29		6.71±1.50		0.149
Platelet count:					
Mean ± SD	166.79±30.39		173.14±24.31		0.394
RDW (%):					
Mean ± SD	13.95±1.66		14.86±2.27		0.528
MPV (fL):					
Mean ± SD	8.28±1.22		7.29±1.11		0.056
PCT (ng/ml):					
Mean ± SD	1.61±0.48		2.19±0.34		0.003

WBC : White blood cell.
PDW : Platelet distribution width.
NLR : Neutrophil-to-lymphocyte ratio.
RDW : Red cell distribution width.
MPV : Mean platelet volume.
PCT : Procalcitonin.
p-value considered significant when >0.05.

Table (3): Correlation between PCT and other markers.

Parameters	PCT (ng/ml)	
	r	*p*-value
Age	–0.066	0.649
WBC (10^6/µL)	0.092	0.526
NEU (%)	0.099	0.494
CRP	0.279	0.048
PDW	0.061	0.675
NLR	0.232	0.105
PLR	0.161	0.263
RDW (%)	–0.045	0.755
MPV (fL)	.115	.426

WBC : White blood cell.
PDW : Platelet distribution width.
NLR : Neutrophil-to-lymphocyte ratio.
RDW : Red cell distribution width.
MPV : Mean platelet volume.
PCT : Procalcitonin.
p-value considered significant when >0.05.

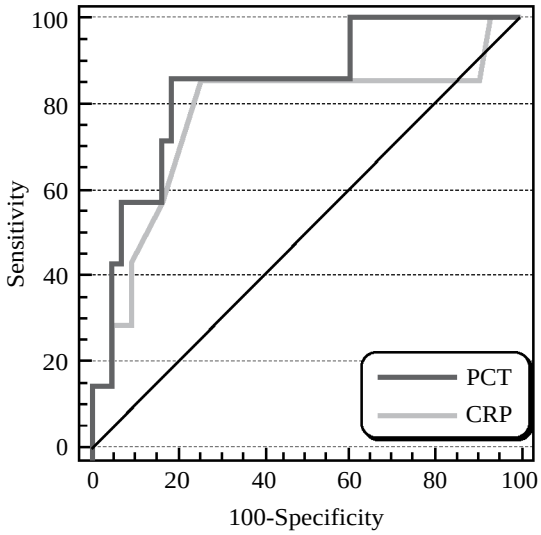

Fig. (1): ROC analysis of PCT and CRP.

Table (4): Logistic regression analysis of PCT and CRP.

	B	S.E.	Wald	Df	Sig.	Exp (B)	95% C.I. for EXP(B)	
							Lower	Upper
CRP	0.226	0.169	1.776	1	0.183	1.253	0.899	1.746
PCT	5.644	2.403	5.515	1	0.019	282.55	2.544	31383.51

p-value considered significant when >0.05.

Discussion

AA is the most prevalent abdominal surgical emergency. While developments in computed tomography and ultrasound have increased diagnosis accuracy, determining the difference between mild and complex appendicitis, which is defined as appendicitis with abscess, gangrene, or perforation, remains complicated **[15]**.

Despite the availability of sophisticated laboratory and imaging diagnostic procedures, the most common ways of identifying AA are in-hospital surveillance and recurrent clinical examination. Despite these attempts, the NAR has been discovered to be as high as 44%. Several biochemical tests, such as CRP, TLC, interleukin6 (IL6), and PCT, have been used to improve the clinical diagnosis of AA **[16]**.

Vaziri et al., **[9]** study included 100 patients, 75 men (75%) and 25 women (25%) with an average age of 28 years, underwent open appendectomy (range 15-60 years). In 59 patients, the PCT level was less than 0.5ng/ml, indicating that the test was negative. There were 27 individuals with a serum PCT value of 0.5-2ng/ml, 9 with a value of 2-10ng/ml, and 5 with a value greater than 10ng/ml among the remaining 41 patients. A PCT value greater than 10ng/ml was found in five of the nine patients with peritonitis, whereas four had a value between 2 and 1 0ng/ml. One patient had a PCT value greater than 10ng/ml, four had a PCT value between 2 and 10ng/ml, and one had a negative PCT value among six cases of surgical site infection.

Moreover, Biradar and Patil **[17]** there were a total of 82 patients, 53 (64.6%) of whom were men and 29 (35.4%) of whom were women. The average age of the 82 people in our study was 25.9 ±11.5 years. Prior to surgery, 65 patients (79.3%) were diagnosed with AA, whereas 17 patients (20.7%) had appendicular perforation. In both AA and appendicular perforation, mean levels of CRP, PCT, and bilirubin were shown to be higher.

A number of laboratory tests can be used to determine the severity of AA. To distinguish between uncomplicated and severe appendicitis, clinical or laboratory indicators such as TLC, body temperature (BT), neutrophil/lymphocyte ratio (N/L ratio), and CRP level have been utilized (20). In 1993, Assicot et al., **[18]** Patients with sepsis and other clinically severe bacterial infections have much greater amounts of plasma PCT, according to the study.

A few other studies have found minimal evidence that PCT elevation can be utilized to identify AA, particularly in children and adolescents. c **[19]** found PCT levels greater than 0.5ng/ml were found in 13% of their pediatric patients with acute appendicitis (PCT sensitivity: 28%), suggesting that PCT is neither predictive nor diagnostic. This finding was also validated in other study conducted by Blab et al., **[20]** who looked through 233 cases of pediatric appendicitis for numerous diagnostic criteria (mean age of 10.47 years). In contrast to our study, another study of Sand et al., **[21]** PCT measurement has been shown to be a good indication of disease severity and a predictive sign of acute appendicitis complications, resulting in surgical exploration in persons with PCT values >0.5ng/ml.

In a prospective study carried by Chandal et al., **[22]** serum PCT was found to be a stronger predictor of acute appendicitis than serum CRP and other assays in forty children aged 5 to 15 years old in India. According to the authors, when accompanied with valid clinical signs and symptoms, serum PCT is an effective diagnostic marker for the illness and should be used in juvenile appendicitis patients to avoid unnecessary appendectomies.

In a prospective study carried by Kaya et al., **[23]** the diagnostic value of PCT, D-dimer and CRP in acute appendicitis was investigated. Because of their low sensitivity and diagnostic utility, they came to the conclusion that D-dimer and PCT are not better markers than CRP for diagnosing AA.

In addition to the aforementioned findings, In our study, the best cutoff value was 1.07ng/ml, or 30mg/l. For diagnosing CAA patients, PCT had a sensitivity and specificity of 85.71% and 81.4%, respectively, whereas CRP had a sensitivity and specificity of 85.71% and 74.42%. CRP has a good positive probability ratio and could be utilized as a rule-in diagnostic tool for AA. Despite its low diagnostic value for AA in general, PCT detected complicated AA with high accuracy.

Vaziri et al., **[9]** reported that for detecting AA, The sensitivity and specificity of PCT level testing are 44% and 100%, respectively. The sensitivity and specificity for detecting peritonitis and surgical site infection, respectively, were 100% and 65%, and 83% and 62%. The NPV and PPV of PCT for appendicitis were 0.1 (10%) and 1 (100%), respectively.

In a systematic review of Yu et al., 2013, A total of seven studies from seven different nations were deemed to be eligible (1011 suspected cases, 636 confirmed). PCT had bivariable pooled sensitivity and specificity of 33 (95 percent confidence interval) (21 to 47) and 89 (78 to 95) percent, respectively, while CRP had 57 (39 to 73) and 87 (58 to 97) percent, and WBC had 62 (47 to 74) and 75 (55 to 89) percent. According to ROC curve study, CRP had the best accuracy (area under ROC curve 075, 95 percent c.i. 071 to 078), followed

by WBC (072, 068 to 076), and PCT (065, 061 to 069). PCT was found to be more reliable in detecting complex appendicitis, with a pooled sensitivity of 62 (33 to 84 percent) and specificity of 94 (90 to 96 percent) **[24]**.

According to the study of Yamashita and his colleges **[25]** the optimal cut-off levels for PCT and CRP were 0.46ng/mL and 6.7mg/dL, respectively. PCT had the same AUC and NPV as CRP, the inflammatory indices with the highest values among the five, although its PPV (73%) was higher than CRP's (48%) **[25]**. We discovered that PCT elevation remained an independent marker for CAA (p=0.019) after adjusting for significant confounding variables.

This is similar to Yamashita et al., **[25]**. In a univariate assessment of the predictors of abscess and/or perforation, PCT 0.46ng/mL had the greatest odds ratio (30.3 [95 percent confidence interval: 6.5-140.5] against PCT 0.46ng/mL) among the five indices evaluated **[25]**.

It's worth noting that the current study's conclusions were reached with various limitations in mind. First, we had a tiny sample size, so we couldn't draw any broad conclusions. Second, determining such characteristics is costly and time-consuming, which might be a significant period of time in an emergency room. Finally, it's possible that PCT levels won't rise significantly until 8-12 hours. As a result, serum PCT may not correctly represent the clinical severity of early emergency department admissions.

Conclusion:

PCT levels can be assessed as a predictor in patients with complicated acute appendicitis. Which is strongly indicated in patients with PCT levels greater than 0.5ng/ml.

Limitations of this study:

Limitations of this study represented in small number of patients and this study was not a multicentric study as it was limited to our department.

Conflict of interest:

No conflict of interest has been declared.

Authors' contribution:

All authors had equal role in design, work, statistical analysis and manuscript writing.

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دور البروكلسيتونين فى التبنأ بحالات التهاب الزائدة المضاعفة

يمثل التهاب الزائدة الدودية حوالى من ٧ إلى ١٠٪ فى المجتمع ويكون العقد الثانى والثالث من العمر أكثر الحالات شيوعاً. يعتبر استئصال الزائدة الدودية هو العلاج الأساسى للالتهابات المصاحبة للزائدة الدودية خلال القرن الماضى. هناك اتجاه حديث لعلاج التهاب الزائدة الدودية الغير مضاعف تحفظياً وذلك لتجنب آثار الجراحة مثل التهاب الجرح والانسداد المعوى والفتق الجراحى. يعتبر البروكلسيتونين من معاملات الالتهاب الهامة فى تشخيص. الالتهاب البكتيرى وليس لمرضى الالتهاب الفيروسى.

الهدف من البحث : يهدف هذا البحث إلى تقييم دور البروكلسيتونين عن طريق قياس نسبته فى الدم بالتنبؤ بحدوث التهاب مضاعف بالزائدة الدودية.

الاستنتاج : يعتبر البروكلستيونين عا مل التهابى بكتيرى عام فى تشخيص حالات التهاب الزائدة الدودية المضاعف عندما تكون نسبته فى الدم أعلى من ٠.٠٥.