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The Diagnostic Value of sCD14-ST (Presepsin) in Acute Appendicitis

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Abstract

Background: Current evidence indicates that sCD14-ST (presepsin) is increased in sepsis. However, the potential role of presepsin for diagnosing appendicitis remains unclear. This study aims to investigate the diagnostic value of presepsin in patients with appendiceal inflammation.

Materials and Methods: This prospective, multi-center study was conducted between August 2015 and December 2017, including 41 patients with suspected appendicitis and 41 controls. Blood samples were collected to assess presepsin, C-reactive protein, fibrinogen, white blood cells, neutrophils, creatinine and gamma-glutamyl transferase. Patients underwent appendicectomy, and specimens were sent for histopathology. A receiver operating characteristic curve assessed the optimal cutoff, sensitivity, and specificity of presepsin to diagnose appendicitis.

Results: In patient group, pathology was positive for appendicitis in 92.7% (catarrhoic: 19.5%, suppurative: 36.6%, and gangrenous: 36.6%). Peritoneal fluid culture was positive in 17.1%, with the most common pathogen being *Escherichia coli*. Presepsin levels were elevated to appendicitis group in comparison with controls ($p<0.001$). There was a statistically significant correlation between presepsin and neutrophils ($r=0.367$, $p=0.018$) among appendicitis patients. Moreover, presepsin levels were marginally related to pathology ($p=0.060$), but gangrenous appendicitis patients had significantly higher levels of presepsin in comparison to suppurative ones. According to ROC analysis, presepsin can predict the inflammation of the appendix with 81% sensitivity and 76% specificity (cutoff 200.5 pg/ml, AUC 0.858 [SE: 0.039; 95% CI: 0.78-0.94; $p<0.001$]).

Conclusion: Serum presepsin is a valuable, diagnostic parameter to predict inflammation of appendiceal appendage, especially for gangrenous cases. However, larger studies are needed to evaluate sCD14-ST in early stages of appendicitis.

Keywords: Presepsin; sCD14-ST; Appendicitis; Gangrenous appendicitis; Diagnosis; ROC analysis

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Abbreviations

AA: Acute Appendicitis; WBC: White Blood Cells; CRP: C-Reactive Protein; PCT: Procalcitonin; LPS: Lipopolysaccharide; LBP: LPS-Binding Protein; SIRS: Systemic Inflammatory Response Syndrome; γGT: Gamma-Glutamyl Transferase; SD: Standard Deviation; ROC: Receiver Operating Characteristic; AUC: Area Under the Curve; CI: Confidence Interval; IL-6: Interleukin 6; IQR: Interquartile Range; 5-HIAA: 5-Hydroxyindoleacetic Acid

Introduction

Acute Appendicitis (AA) is one of the most frequent surgical emergencies, with an incidence of approximately 90 to 100 cases per 100,000 people, annually, in the developed world. There is a slight male preponderance, and the incidence peaks in the second or third decade of life. However, accurate diagnosis or exclusion of AA remains challenging [1], particularly among female patients of reproductive age, obese, elderly, and pediatric patients [2]. This is demonstrated by negative appendectomy cases, ranging between 10% and 34% [3]. The diagnosis of AA, that has to be as early as possible in the suspected patients, is mainly based on history, physical examination, and laboratory testing [2]. Diagnostic laparoscopy and imaging aid in AA's diagnosis [1], but they are not always

available. The Alvarado score, the most common of the various in-use scores, has good sensitivity but low specificity [4]. Additionally, various diagnostic biomarkers such as, White Blood Cells (WBC), C-Reactive Protein (CRP), and Procalcitonin (PCT) have been used. Due to the inaccuracy of the above parameters, a meta-analysis noted the need to discover new markers for diagnosing suspected appendicitis [5]. The ideal biomarker should be of high sensitivity and specificity, leading to a fast, accurate diagnosis and fewer negative explorations [6], while being of low cost and readily available. CD14 is expressed on monocytes and macrophages, and works as a receptor for Lipopolysaccharide (LPS) and LPS-Binding Protein (LBP). CD14 activates a cascade of proinflammatory signaling molecules, when interacts with infectious agents, and is shed into the circulation as soluble CD14 (sCD14), where plasma proteases generate a 13-kDa N-terminal fragment called sCD14 Subtype (sCD14-ST) or presepsin [7]. Healthy individuals have very low levels of presepsin, which can be increased in response to bacterial infections, depending on severity [8]. Presepsin levels differ significantly between healthy subjects and patients with localized infection, Systematic Inflammatory Response Syndrome (SIRS), sepsis, or severe sepsis [8,9]. Presepsin can be used in the emergency department as a marker for the initial diagnosis of infection [10]. For abdominal conditions, presepsin has already shown potential in the diagnosis of abdominal sepsis [11]. However, the role of presepsin in the diagnosis of AA is still unclear, with only three recent studies [12-14] assessing presepsin in patients with AA. Therefore, we hypothesized that presepsin levels would be a useful predictor biomarker of appendicitis. This study aims to investigate presepsin in diagnosing acute appendicitis.

Materials and Methods

Study design and setting

This clinical, prospective, observational, cohort study was conducted at two different surgical departments, in two hospitals. Consecutive patients, admitted to the departments for suspected appendicitis from August 2015 to December 2017, were enrolled. The study was approved by the Ethics Committee according to the principles of Declaration of Helsinki. Written informed consent was obtained from all patients. Assent was also obtained from patients under 18 years, with written informed consent from their parents or legal guardians.

Study population

All patients with suspected appendicitis (n=41) meeting the following criteria were enrolled: Right lower quadrant pain, compatible laboratory and imaging results with AA and surgery up to 72 h after admission. The exclusion criteria were: Age less than 14 years, pregnant women, alcoholics, use of contraceptive pills, prior history of appendicitis and chronic kidney disease. Patients underwent open or laparoscopic appendectomy. Also, all patients received a preoperative single-dose of antibiotic. The control group (n=41) included patients admitted to surgical or internal medicine department with no signs or symptoms of active infection (e.g., patients undergoing surgical hernia repair).

Measurements

CRP, fibrinogen levels, WBC, neutrophil counts, creatinine, and Gamma-Glutamyl Transferase (γGT) were measured. Standardized reference values of our hospitals' biochemistry laboratory for normal CRP (0 mg/dl to 0.3 mg/dl), WBC (4 K/μL to 10.8 K/μL), neutrophils (42.2% to 75.2%, 1.8 K/μL to 7 Kμ/L), fibrinogen (180 mg/dl to 350 mg/dl), creatinine (0.55 mg/dl to 1.02 mg/dl) and γGT (5 U/L to 55 U/L) were accepted for this study design. All appendectomy specimens were sent for pathology examination. Additionally, blood samples were cultured for Gram positive and negative bacteria. A chemiluminescent enzyme immunoassay to measure presepsin concentration in venous blood was used (PATHFAST®, Presepsin analyzer; Mitsubishi Chemical Medience Corporation, Tokyo, Japan) [15]. The results were obtained in 15 min. Presepsin levels were expressed as pg/mL. All the data were entered into an Excel format for statistical analysis.

Statistical analysis

Continuous variables were presented in mean ± Standard Deviation (SD) or median and Interquartile Range (IQR) while, categorical variables were expressed in percentages. The normality of the distribution was checked using the Kolmogorov-Smirnov test. Comparisons between groups' demographic characteristics were performed using t-test and Mann-Whitney. Correlation between quantitative variables was examined using Spearman's correlation coefficient. A Receiver Operating Characteristic (ROC) analysis was conducted, and the Area Under the Curve (AUC) with 95% Confidence Interval (CI), sensitivity, and specificity of different cutoff points were estimated. All tests were two-sided and statistical significance was set at $p<0.05$. The statistical package SPSS vr 21.00 (IBM Corporation, Somers, NY, USA) was used for all statistical analyses.

Results

Demographic and clinical characteristics

The study population consisted of 41 (50%) controls and 41 (50%) patients with suspected acute appendicitis. 49 (59.8%) were males, and 33 (40.2%) were females, with a mean age of 33.4 ± 16.1 years, with a minimum age of 16 years, and a maximum age of 85 years (Table 1). Only 2.4% had a positive blood culture. Pathology was negative in 7.3%, while 19.5% had catarrhoic, 36.6% suppurative, and 36.6% gangrenous appendicitis. Peritoneal fluid culture was negative in 75.6% of patients, while the most common pathogen, that was identified, was *Escherichia coli*. When comparing the two groups (Table 2), we found no statistically significant difference regarding the distribution of genders (p=0.496) and age (p=0.619), which reflects the homogeneity between the groups. Regarding presepsin, there was a statistically significant difference between the groups with either parametric ($p<0.001$) or non-parametric analysis ($p<0.001$). To be specific, we found median presepsin levels of 139.0 pg/ml (112.5 IQR) *vs.* 324.0 pg/ml (375.0) for controls versus AA patients, respectively.

Presepsin correlations and ROC analysis

Among patients with appendicitis, there was a statistically significant correlation between presepsin and neutrophils (r=0.367, p=0.018) (Table 3). Additionally, presepsin was not significantly correlated with age (r=0.053, p=0.740), WBC (r=0.111, p=0.488), CRP (r=0.173, p=0.280), creatinine (r=0.026, p=0.870), γGT (r=0.089, p=0.581), and fibrinogen (r=0.117, p=0.467). There was also no statistically significant difference between genders (p=0.862) in relation to presepsin, while there was a marginal difference in relation to pathology (p=0.060). Pair comparisons showed a difference of gangrenous compared to catarrhoic (p=0.076; marginal) and suppurative appendicitis (p=0.033; significant), while there was no significant difference between catarrhoic and suppurative appendicitis (p=0.975). According to the ROC analysis, presepsin

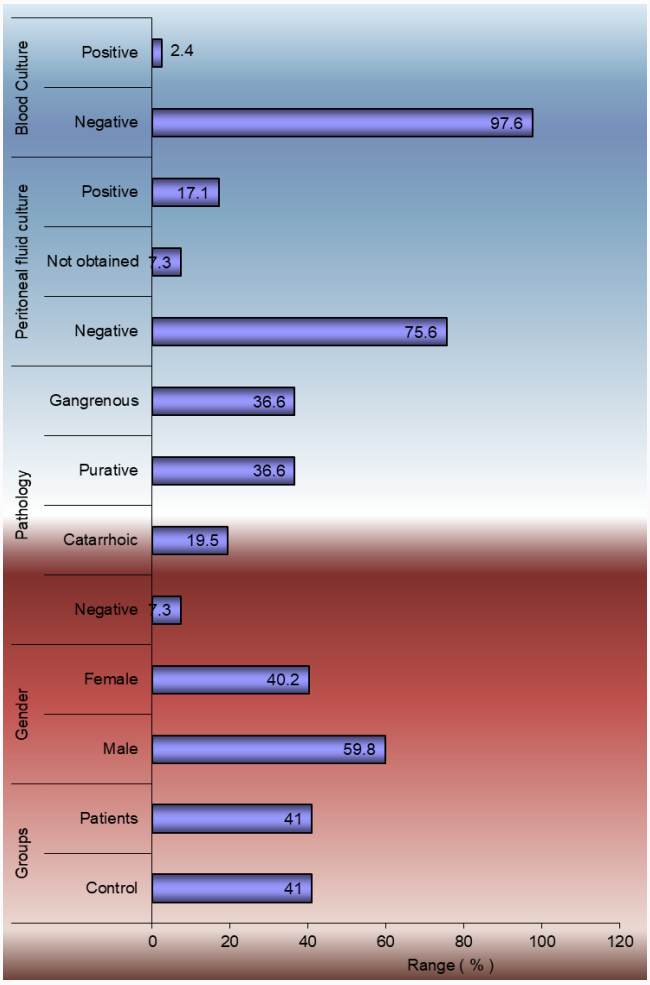

Figure 1: Receiver Operating Characteristic (ROC) curve analysis for patients with acute appendicitis using presepsin.

levels can predict the inflammation of appendiceal appendage with AUC 0.858 [SE: 0.039; 95% CI: 0.78-0.94; p<0.001] (Figure 1). The best cutoff that maximizes sensitivity and specificity is 200.5 pg/ml, with 81% sensitivity and 76% specificity (Table 4).

Discussion

In the present study, we evaluated whether the levels of serum presepsin can differentiate patients with and without appendicitis. Higher presepsin levels were found in patients with appendicitis compared to the control group. There was a statistically significant correlation between presepsin and neutrophils, and presepsin levels were higher in gangrenous compared to catarrhoic and suppurative appendicitis. According to the ROC analysis, a presepsin cutoff of 200.5 pg/ml results in 81% sensitivity and 76% specificity. Diagnosing appendicitis remains a surgical challenge, as negative appendicectomy ranges between 10% and 34%, and diagnoses can be missed in about 20% to 40% of cases [3]. Thus, biomarkers such as CRP, WBC, granulocyte count, Interleukin-6 (IL-6), serum amyloid A, riboleukograms, granulocyte colony-stimulating factor, urine leucine-rich α-2-glycoprotein, calprotectin [3], fibrinogen, bilirubin, Procalcitonin (PCT) [16], and oxidative stress markers [12] have been investigated for the diagnosis of AA. These markers aid in the suspicion of AA, however, none of them can reliably predict the diagnosis, and new ones are needed [3,5]. Presepsin is a new,

Table 1: Demographics of control and patient groups.

			N	%
Groups	Control		41	50.0
	Patients		41	50.0
Gender	Male		49	59.8
	Female		33	40.2
Age	Mean ± SD (Min-Max)		33.40 ± 16.1	
Pathology	Negative		3	7.3
	Catarrhoic		8	19.5
	Purutive		15	36.6
	Gangrenous		15	36.6
Blood culture	Negative		40	97.6
	Positive		1	2.4
Peritoneal fluid culture	Negative		31	75.6
	Not obtained		3	7.3
	Positive N=7	*Staphylococcus warneri*	1	17.1
		Staphylococcus epidermidis	1	
		Staphylococcus aureus	1	
		Streptococcus anginosus	1	
		Enterobacter aerogenes	1	
		Escherichia coli	2	
		Staphylococcus caprae	1	
		Staphylococcus hominis	1	
		Bacterodes fragilis	1	
WBC	Mean ± SD (Min-Max)		13.25 ± 3.63 (6.6-25.2)	
Neutrophils			80.9% ± 8.8 (64.5-95.0)	
Creatinine			1.0 ± 0.3 (0.6-1.9)	
Fibrogen			366.43 ± 87.61 (225.9-611.5)	
CRP	Median (IQR) (Min-Max)		4.0 (8.1) (0.1-34.1)	
γGT			19.0 (8.0) (12.0-74.0)	

WBC: White Blood Cells; CRP: C-Reaction Protein; γGT: γ-Glutamyl Transferase; SD: Standard Deviation; IQR: Interquartile Range

emerging, sensitive and specific biomarker, and its high levels can detect infection and sepsis in early stages [9,17]. It was found to be the most predictive biomarker for sepsis, followed by CRP, IL-6, and PCT [9]. Endo reported that presepsin levels are significantly higher among patients with systemic or localized bacterial infection compared to those with non-bacterial infections [8]. Presepsin values may be able to risk-stratify patients with different sepsis severity [9,17,18]. It is also predictive of mortality and aids in monitoring response to therapy among patients with sepsis [19]. Studies have investigated presepsin in various inflammatory conditions besides sepsis, including abdominal ones [20,21]. In acute surgical diseases, including AA, an increase of intra-abdominal pressure leads to an increase of presepsin, aiding in the stratification of patients that need emergency surgery [22]. Higher baseline presepsin levels were found among patients with abdominal or urinary tract infections in comparison to those with lung infections [19]. In a study by Novelli presepsin demonstrated 100% sensitivity for bacterial infection among abdominal surgery and transplant patients, confirmed by blood cultures [23]. Regarding patients with acute abdominal conditions, presepsin is a sensitive

Table 2: Homogeneity between groups.

		Control	Patients	p-value
Gender: Male/Female (n%)		23 (56,1%)/ 18(43,9%)	26 (63.4%)/ 15(36.5%)	0.496
Age: Mean ± SD		32.77 ± 15.3	34.59 ± 17.6	0.619
sCD14-ST	Mean ± SD	153.92 ± 84.13	505.90 ± 528.81	<0.001
	Median (IQR)	139.0 (112.5)	324.0 (375.0)	<0.001

SD: Standard Deviation; IQR: Interquartile Range

Table 3: Correlation between sCD14-ST and demographic/biochemistry indexes.

	sCD14-ST (pg/mL)	
	Spearman Correlation	*p-value*
Age	0.053	0.740
WBC	0.111	0.488
Neutrophils	***0.367***	***0.018***
CRP	0.173	0.280
Cr	0.026	0.870
γGT	0.089	0.581
Fibrogen	0.117	0.467
	Median (IQR)	*p-value*
Gender: Male/Female	303.5(420.8)/355.0(349.0)	0.862
Pathology: gangrenous/catarrhoic/ purulent	**453** (844)/**213**(371.3)/**281**(202)	***0.060***

WBC: White Blood Cells; CRP: C-Reaction Protein; Cr: Creatinine; γGT: γ-Glutamyl Transferase; IQR: Interquartile Range

Table 4: ROC analysis of appendix inflammation.

	AUC	SE	95% CI		p-value	Cut-off point	Sensitivity	Specificity
sCD14-ST	0.858	0.039	0.78	0.94	<0.001	200.5	81%	76%

* Higher values denote appendix inflammation
AUC: Area Under the Curve; SE: Standard Error; CI: Confidence Interval

and fast indicator of abdominal sepsis, more predictive than PCT, CRP, or WBC count [11]. Presepsin was prognostic of source control in abdominal sepsis and clinical course of enterocutaneous fistulas [20]. Presepsin also showed a specificity of 98.63% in determining gastrointestinal anastomotic leak [21]. Although presepsin has been studied in sepsis and abdominal inflammatory conditions, only three recent studies have investigated its role in AA. In 2018, Ozer found that inflammatory and oxidative stress markers were significantly altered in 65 AA patients compared to 65 controls. Serum presepsin, CRP, WBC count were elevated in patients versus controls ($p<0.05$). However, only Alvarado scores were higher in perforated versus non-perforated appendicitis [12]. In our study, presepsin levels were also significantly elevated among appendicitis patients compared to controls ($p<0.001$). In 2020, Binboga found that serum levels of presepsin, WBC, CRP, and neutrophil/lymphocyte ratio were significantly higher in complicated versus uncomplicated appendicitis. All those parameters were significant for predicting complicated AA. Presepsin's AUC was larger than that of WBC, CRP, and neutrophil/lymphocyte ratio, with a 272 pg/ml cutoff. Serum presepsin levels had a median of 20.0 pg/ml (min 7.0 pg/ml - max 122.0 pg/ml) *vs.* 133.5 pg/ml (3.0 pg/ml to 1310.0 pg/ml) for controls versus AA patients, respectively [13]. Our study found median presepsin levels of 139.0 pg/ml (112.5 IQR) *vs.* 324.0 pg/ml (375.0) for controls versus AA patients, respectively. Our cutoff point for predicting appendicitis (200.5 pg/ml) is logically lower than 272 pg/ml, which predicts complicated appendicitis. Additionally, our study similarly found a marginally significant increase in presepsin levels as histological stages progress. We observed significant difference in presepsin levels between suppurative and gangrenous stages of acute appendicitis. The recent study of 2022 investigated the role of presepsin in AA diagnosis, exclusively in pediatric patients. It is the only published study that reports no differences in presepsin levels between patient and control group, fact that is contradictory to the other studies. Also, this study found no correlation between presepsin levels and pathology stage of AA. However, we have to mention that this study has a very strong limitation as its sample is not homogeneous (AA patients: 94 – healthy patients: 102) [14]. In our study, we concluded that presepsin levels were higher in AA group and we found increased levels of presepsin to patients with gangrenous appendicitis. It is mandatory further studies to investigate the diagnostic role of presepsin in children with suspected AA. According to Liu a 317 pg/ml threshold of presepsin was best for predicting infection [24]. Our cutoff was found best at 200.5 pg/ml for predicting appendicitis. Presepsin levels increase with age and in cases of impaired renal function [25].

However, our study found no correlation between age or sex and presepsin levels. Likewise, in a study with severe sepsis and septic shock patients during their first week of intensive care stay, presepsin levels were also not correlated with age or sex [26]. For catarrhoic, suppurative, and gangrenous appendicitis, we found presepsin levels of median 213 pg/ml (IQR 371.3), 281 pg/ml (IQR 202), and 453 pg/ml (IQR 844), respectively; reflecting the clinical course of disease, as presepsin does in sepsis patients [13]. Our 200.5 pg/ml cutoff maximizes sensitivity and specificity. Sensitivity seems better than the most used markers, such as WBC, CRP, bilirubin, PCT, IL-6, and 5-Hydroxyindoleacetic Acid (5-HIAA). Specificity seems adequate, but smaller in comparison to PCT, bilirubin and 5-HIAA [16]. Interestingly, we found a statistically significant correlation of presepsin levels with neutrophil count in patients with appendicitis, but not with WBC or CRP. This correlation may reflect neutrophil stimulation following CD14 receptor activation [7]. Similarly, Song found a statistically significant correlation of presepsin levels with CRP, but not with WBC in patients with enterocutaneous fistula complicated by abdominal sepsis. However, patients with high presepsin levels had significantly high levels of CRP and WBC [20]. A number of limitations of our study should be mentioned. First, presepsin was not compared to other biomarkers such as IL-6 or PCT and was not measured daily. Second, our study had a relatively small sample size and may be underpowered. The strengths of this study are its prospective design, its statistically homogeneous sample groups, and that it is the first multicenter study. Moreover, we included the patients with negative histopathology to our sample group in order to use ROC analysis and examine accurately the sensitivity and specificity of presepsin, increasing the power of our study results.

Conclusion

Serum presepsin levels were significantly higher in patients with appendicitis compared to controls. sCD14-ST is a useful, very promising biomarker that can help diagnose appendicitis in clinical practice, similar to other inflammation markers. Presepsin levels above 200.5 pg/ml can predict appendicitis with 81% sensitivity and 76% specificity. However, further and larger studies are needed to evaluate presepsin in inflammation of appendiceal appendage and investigate new and specific biomarkers for AA's diagnosis.

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