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The Role of C-reactive Protein in Diagnosis of Acute Complicated Appendicitis: A Diagnostic Accuracy Study

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Abstract

Introduction: Acute appendicitis is one of the most common emergencies of general surgery. Contrary to simple appendicitis, the complicated cases are associated with higher morbidity and mortality. Except for pathology, no accurate diagnostic test has been found to identify complicated cases.

Objective: Here in, we aim to evaluate the serum C-Reactive Protein (CRP) level in both acute simple and complicated appendicitis.

Methods: In this diagnostic accuracy study, 199 patients with acute appendicitis were enrolled. The serum CRP level was evaluated in patients. Post-operatively, the patients were divided into simple and complicated appendicitis based on histopathological examination. Eventually, analysis of the CRP level and type of appendicitis was performed.

Results: Fifty-three patients were categorized into complicated appendicitis and 146 patients into simple appendicitis. The median of CRP was significantly higher in the complicated group. Additionally, the optimal cutoff point was as follows: [65.0 (25.0) vs 25.0 (51.0); P-value< 0.001]. The optimal cutoff point for CRP was more than 42 with 81.1% sensitivity (95% CI: 68.0 to 90.6), and 67.8% specificity (95% CI: 59.6 to 75.3). The positive (PPV) and negative predictive values (NPV), based on the prevalence of complicated appendicitis (26.6%) for optimal cutoff point, were 47.8% (95% CI: 37.1 to 58.6) and 90.8% (95% CI: 83.8 to 95.5).

Conclusion: Our study revealed that evaluation of serum CRP levels could be useful and beneficial in the diagnosis of acute complicated appendicitis.

Key words: Appendicitis; Complications [Subheading]; C-Reactive Protein; Diagnosis

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INTRODUCTION

Acute appendicitis is one of the most common emergencies of general surgery with a lifetime prevalence of 7%, accounts for approximately 10% of all emergency acute abdominal surgeries (1-3). It is classified into two subgroups of simple and complicated appendicitis. In the case of simple appendicitis, the likelihood of surgical complication, duration of hospitalization and rehabilitation would significantly be shortened. In contrast, complicated appendicitis (perforation, gangrenous, appendiceal mass or phlegmon) is highly associated with increased rate of morbidity and mortality, especially in the elderly (4-9).

Due to diverse clinical outcome of appendicitis, it is of paramount of importance to differentiate between two simple and complicated cases. Regarding the advanced laboratory and imaging techniques, the early diagnosis and consequent appropriate therapy are facilitated. However, there are still some limitations in identifying complicated cases; except for pathology, there is no accurate diagnostic test to identify complicated cases. The laboratory parameters as white blood cell count (WBC), neutrophil / lymphocyte ratio (N/L ratio), and C-reactive protein (CRP) level, have been introduced in this regard (10). CRP is an inflammatory marker, which is synthesized by the liver, in response to interleukins and cytokines produced by macrophages. In response to acute infection or inflammatory process, the CRP level dramatically increases, peaking at 48 hours, with a constant half-life of approximately 19 hours (11). The role of CRP in early diagnosis of appendicitis has been confirmed in the literature, and some have advocated the high sensitivity of CRP to assess the risk of complication development in acute

appendicitis. However, the serum CRP level, indicating the complicated appendicitis is still unclear (12-16). Here in, we aim to evaluate the serum CRP level in both acute simple and complicated appendicitis, in order to establish the diagnostic value of serum CRP level in both diagnosis and prediction of further complicated appendicitis.

METHODS

Study design and setting

This diagnostic accuracy study was performed from July 2018 until March 2019 in Poursina hospital, Rasht, Iran. The study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1397.105). In addition, written informed consents were obtained from all patients prior to their inclusion in this study.

Study population

The inclusion criterion was the patients with acute abdominal pain, referring to our center with an Alvarado score ≥ 5. Patients with a history of recent infection, burning or inflammatory process, the underlying collagen vascular disease or cancer, were excluded. Considering 1-α=0.95 and 1-β=0.90 and possible prevalence of complicated appendicitis equal to 33%, sample size calculated as 199 cases. Patients with acute appendicitis were enrolled in the study, using consecutive sampling.

Definition

The diagnosis was based on the Alvarado scoring system, which is based on 6 clinical features (abdominal pain migrating to the right iliac fossa, anorexia, nausea or vomiting, tenderness in the right iliac fossa, rebound tenderness and fever), and 2 laboratory investigations (WBC count and neutrophil shift). Two points have been assigned to tenderness and leukocytosis and one point each for the six other items, for a total score of ten points. A score of 5 or 6 is in line with the clinical diagnosis of acute appendicitis (17).

Data gathering

In the following, a checklist including the patients' characteristics such as age, sex, Alvarado score, pre-operative WBC count, pre-operative CRP level (Normal level < 8 mg/dL), and radiologic findings either sonography or abdominal computed topography (CT), was fulfilled. Then, the patients underwent appendectomy, and the definitive histological result was recorded for each patient who had a complete pre-operative checklist. According to the results of histopathological examination and radiologic findings, patients were divided into two groups, including uncomplicated inflamed appendicitis and complicated appendicitis (perforated or gangrenous appendicitis, appendiceal mass or phlegmon).

Statistical analysis

The values of demographic and clinical variables were expressed as number with percentage for categorical variable; median with interquartile range (IQR), presented as a range of 25th–75th percentiles, and numerical variable, demonstrated as mean with standard deviation (SD). We used Chi-square and Fisher's exact test for comparison of categorical variables. For comparison of numerical variable in two appendicitis groups, first, we checked the normality assumption with Kolmogorov–Smirnov test, and then the independent T-test was applied to compare the WBC count, and Mann-Whitney U test for CRP, Polymorphonuclear (PMN) and Alvarado score in two groups. The accuracy of CRP for discrimination of acute complicated appendicitis was evaluated by receiver operating characteristics' (ROC) analysis. We calculated the sensitivity and specificity with 95% confidence interval (CI) for all CPR cutoff points. The, optimal cutoff point was chosen based on the maximum Youden index J. In addition, positive (PLR) and negative likelihood ratios (NLR) were calculated for the cutoff points. The positive (PPV) and negative predictive values (NPV) of cutoff points with 95% CI were estimated based on the prevalence of complicated appendicitis. Statistical analysis of the data was performed, using Statistical Package for the Social Sciences (SPSS, version 21) and Stata v.12.

RESULTS

Among the 199 study patients with acute appendicitis, 53 patients (26.6%) were categorized into complicated appendicitis and 146 patients (73.4%) into simple appendicitis. Demographic and clinical features of the patients with appendicitis are reported in table 1. The mean was 30.7±13.1 years. The mean age of complicated appendicitis group was significantly greater than the simple appendicitis group (35.6 ±14.3 vs 28.9 ±12.2, p-value= 0.003). In terms of gender, 67.9% and 57.5% of the complicated and simple appendicitis were male, respectively (p-value = 0.185). Regarding the clinical examination, there was a significant association between severity of rebound tenderness with complicated appendicitis (p-value = 0.001). Furthermore, no statistical difference was found between the right lower quadrant tenderness and right lower quadrant pain, nausea, vomiting and types of appendicitis (p-value >0.05). In contrast, in terms of anorexia and

Table 1: Demographic and clinical features of the study patients with appendicitis

Variable	Total (n=199)	Appendicitis group		P-value
		Complicated (n=53)	Simple (n=146)	
Gender, n (%)				
Male	79 (39.7)	36 (67.9)	84 (57.5)	0.185
Female		17 (32.1)	62 (42.5)	
Age, year				
Mean (SD)	-	35.6 (14.3)	28.9 (12.2)	0.003
Mini- Max		16.0-80.0	13.0-77.0	
Age categories, n (%)				
<20	38 (19.1)	6 (11.3)	32 (21.9)	0.014
20-29	69 (34.7)	12 (22.6)	57 (39.0)	
30-39	57 (28.6)	20 (37.7)	37 (25.3)	
40-49	17 (8.5)	7 (13.2)	10 (6.9)	
>50	18 (9.1)	8 (15.2)	10 (6.9)	
RlQ pain, n (%)	193 (97.0)	51 (96.2)	142 (97.3)	0.506
Anorexia, n (%)	154 (77.4)	48 (90.6)	106 (72.6)	0.007
Nausea, n (%)	155 (77.9)	44 (83.0)	111 (76.0)	0.293
Vomiting, n (%)	112 (56.3)	32 (60.4)	80 (54.8)	0.483
Fever, n (%)	26 (13.1)	11 (20.8)	15 (10.3)	0.052
RLQ tenderness, n (%)	184 (92.5)	52 (98.1)	132 (90.4)	0.055
Rebound tenderness, n (%)				
No	64 (32.2)	13(24.5)	51 (34.9)	0.001
Mild	31 (15.6)	4 (7.5)	27 (18.5)	
Moderate	93 (46.7)	28 (52.8)	65 (44.5)	
Severe	11 (5.5)	8 (15.1)	3 (2.1)	

RLQ: right lower quadrant

Table 2: Alvarado score, CRP, WBC and PMN percentage in acute appendicitis

Variable	Appendicitis group		P-value
	Complicated (n=53)	Simple (n=146)	
Alvarado score			
Mean (SD)	8.3 (1.3)	7.4 (1.6)	<0.001 [b]
Median (IQR)	9.0 (8.0-9.0)	8.0 (6.8-9.0)	
CRP, mg/L			
Mean (SD)	54.8 (21.5)	32.3 (28.3)	<0.001 [b]
Median (IQR)	65.0 (45.0-70.0)	25.0 (6.0-57.0)	
WBC, per mcL			
Mean (SD)	13500.0 (4225.4)	12577.4 (3345.1)	0.155 [a]
Median (IQR)	13600.0 (10500.0 -17750.0)	12500.0 (10600.0 -14625.0)	
PMN			
Mean (SD)	79.1 (6.8)	68.4 (12.9)	<0.001 [b]
Median (IQR)	79.0 (77.0-84.5)	68.0 (60.0-79.0)	

a: Parametric test; b: Non-parametric test

Abbreviation. SD: Standard Deviation; IQR: Interquartile range was presented with quartile 1 - quartile 3; CRP: C-reactive protein; PMN: Polymorphonuclear; WBC: white blood cell

fever, there was a significant difference between simple and complicated appendicitis (p-value = 0.007, p-value = 0.052, respectively).

Based on Mann-Whitney U test, our results showed that the Alvarado score was considerably higher in the complicated group [Median (IQR): 9.0 (1.0) vs 8.0 (1.2); p-value= 0.001]. In addition, our findings revealed that the median (IQR) of serum CRP level is significantly higher in the complicated group than the simple group [65.0 (25.0) vs 25.0 (51.0); p-value < 0.001]. Furthermore, we showed, although there was not a statistical difference between the two groups in terms of the WBC level (p-value = 0.155), but for PMN differentiation, a considerable difference was evident (p-value = 0.001) (Table 2). In order to identify the acute complicated appendicitis, the area under the ROC Curve (AU-ROC) of CRP variable was measured as 0.727 (Figure 1). Based on the Youden index J, the optimal cutoff point for CRP was more than 42 with 81.1% sensitivity (95% CI: 68.0 to 90.6), and 67.8% specificity (95% CI: 59.6 to 75.3). In addition, positive (PLR) and negative likelihood ratios (NLR) for this cutoff point were 2.52 and 0.28, respectively. The positive (PPV) and negative predictive values (NPV) based on the prevalence of

Table 3: Demographic and clinical features of the study patients with appendicitis

Criterion	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	PPV (95% CI)	NPV (95% CI)
>33	83.02 (70.2 - 91.9)	62.33 (53.9 - 70.2)	2.20 (1.7 - 2.8)	0.27 (0.1 - 0.5)	44.4 (34.5 - 54.8)	91.0 (83.6 - 95.8)
>35	83.02 (70.2 - 91.9)	64.38 (56.0 - 72.1)	2.33 (1.8 - 3.0)	0.26 (0.1 - 0.5)	45.8 (35.6 - 56.3)	91.3 (84.1 - 95.9)
>36	81.13 (68.0 - 90.6)	65.75 (57.5 - 73.4)	2.37 (1.8 - 3.1)	0.29 (0.2 - 0.5)	46.2 (35.8 - 56.9)	90.6 (83.3 - 95.4)
>38	81.13 (68.0 - 90.6)	66.44 (58.2 - 74.0)	2.42 (1.9 - 3.1)	0.28 (0.2 - 0.5)	46.7 (36.3 - 57.4)	90.7 (83.5 - 95.4)
>41	81.13 (68.0 - 90.6)	67.12 (58.9 - 74.7)	2.47 (1.9 - 3.2)	0.28 (0.2 - 0.5)	47.3 (36.7 - 58.0)	90.7 (83.6 - 95.5)
>42*	81.13 (68.0 - 90.6)	67.81 (59.6 - 75.3)	2.52 (1.9 - 3.3)	0.28 (0.2 - 0.5)	47.8 (37.1 - 58.6)	90.8 (83.8 - 95.5)
>43	77.36 (63.8 - 87.7)	68.49 (60.3 - 75.9)	2.46 (1.9 - 3.2)	0.33 (0.2 - 0.6)	47.1 (36.3 - 58.1)	89.3 (82.0 - 94.3)
>45	71.70 (57.7 - 83.2)	68.49 (60.3 - 75.9)	2.28 (1.7 - 3.1)	0.41 (0.3 - 0.6)	45.2 (34.3 - 56.5)	87.0 (79.4 - 92.5)
>46	71.70 (57.7 - 83.2)	69.18 (61.0 - 76.5)	2.33 (1.7 - 3.1)	0.41 (0.3 - 0.6)	45.8 (34.8 - 57.1)	87.1 (79.6 - 92.6)
>47	67.92 (53.7 - 80.1)	71.23 (63.2 - 78.4)	2.36 (1.7 - 3.2)	0.45 (0.3 - 0.7)	46.2 (34.8 - 57.8)	86.0 (78.5 - 91.6)
>48	66.04 (51.7 - 78.5)	71.92 (63.9 - 79.0)	2.35 (1.7 - 3.2)	0.47 (0.3 - 0.7)	46.1 (34.5 - 57.9)	85.4 (77.9 - 91.1)
>50	64.15 (49.8 - 76.9)	71.92 (63.9 - 79.0)	2.28 (1.6 - 3.2)	0.50 (0.3 - 0.7)	45.3 33.8 - 57.3)	84.7 (77.1 - 90.5)

* The optimal cutoff point for CRP

Abbreviation. CI: Confidence Interval; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value

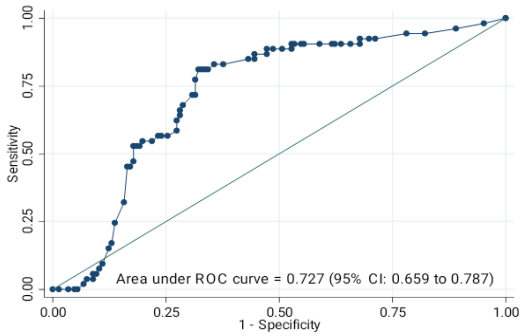

Figure 1: ROC cure and CRP level cutoff point to determine the complicated appendicitis

complicated appendicitis (26.6%) for optimal cutoff point was 47.8% (95% CI: 37.1 to 58.6), and 90.8% (95% CI: 83.8 to 95.5), respectively (Table 3).

Discussion

In current study we found that the serum CRP level may help to differentiating the complicated appendicitis from simple cases. Previous studies have shown that positive CRP could increase both the accurate diagnosis, and differentiation of simple and complicated appendicitis. The study of Tucker et al. reported 327 patients with suspicious acute appendicitis, demonstrating that the average serum CRP level in the complicated appendicitis was higher than the simple appendicitis (129.75 compared to 86.49), and the specificity of CRP as a diagnostic test was significantly higher in the complicated cases (95% compared to 20%). However, the sensitivity was not reported considerable (15). In current study, CRP level was also significantly higher in the complicated appendicitis (p-value < 0.001). In addition, Abdoulhosseini et al. showed that CRP was statistically higher in the perforated appendicitis than simple cases (53.8±15.3 vs 35.6±17.9; p=0.003) (16). Similarly, Moon et al. showed that the serum CRP level in the complicated appendicitis is higher than the simple appendicitis (10.05±10.10 vs 1.82±2.29; p-value < 0.001). Furthermore, the sensitivity and specificity of CRP>7.05 in the complicated appendicitis was 57.6% and 98.3%, respectively (14).

However, the specificity of the CRP was reported significantly higher than our study. Moreover, a vast majority of studies that tested this hypothesis as the studies of Kim et al., Monsvale et al., Tucker et al. and Moon et al., all showed that the higher serum CRP level was associated with more complications and prolonged hospitalization (14, 15, 18, 19).

In Iran, similar studies have been conducted recently. Asfar et al. in a double-blind study

reported the sensitivity and specificity of CRP as 86.6% and 93.6%, respectively, which was similar to one outside of Iran, in terms of specificity (20). Interestingly, Izadi et al. evaluated different subtypes of appendicitis. They revealed, although the CRP level was significantly higher in purulent appendicitis, in comparison to the simple appendicitis, but the CRP level was not statistically different between perforated and simple appendicitis. Eventually, they suggested CRP as a diagnostic method with sensitivity and specificity of 80 and 62%, respectively (21).

Overall, our findings are in line with the previous studies. Note-taking, the cutoff point level of CRP was different in the current literatures, as the study of Monsvale et al. introduced 361.9 nmol/L (38.0 mg/dL) or Moon et al. demonstrated 7.05 mg/dL (67.14 nmol/L) as the cutoff point level for CRP (14, 19), which may arise from the different CRP measurement units.

Limitations

One major limitation of our study is the level of CRP, which was measured at the time of admission, but not serially. Therefore, it is suggested that in the future studies, the level of CRP in the complicated appendicitis patients, undergoing supportive care should be performed several times before surgery.

Conclusions

An accurate diagnosis and consequent appropriate treatment in regard to acute right lower quadrant abdominal pain are crucial. Taking into account all clinical considerations and current paraclinical diagnostic tests, we revealed that evaluation of serum CRP levels could be useful and beneficial in the diagnosis of acute complicated appendicitis.

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Authors' contribution

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

Conflict of interest

None declared.

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