European Review for Medical and Pharmacological Sciences 2022; 26: 8057-8063

Role of hyponatremia in differentiating complicated appendicitis from uncomplicated appendicitis: a comparative study

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Abstract. – OBJECTIVE: Some studies suggest that serum sodium level may decrease at a greater degree in complicated acute appendicitis (CA) because of the increased severity of inflammation. This study aimed to determine the predictive value of some inflammatory markers and hyponatremia in differentiating CA from uncomplicated acute appendicitis (UCA).

PATIENTS AND METHODS: In this retrospective cohort study, the data of patients who underwent urgent appendectomy in Department of General Surgery, Eskisehir Osmangazi University from January 01, 2016 to January 01, 2021, were analyzed. Patients were divided according to appendicitis type, UCA and CA.

RESULTS: In this study, 10.2% (n = 79) of 772 acute appendicitis cases were CA. Multiple logistic regression analysis revealed that high age (p = 0.001), male sex (p = 0.014), high leukocyte count (p = 0.045), low lymphocyte count (p = 0.023) and hyponatremia (p <0.001) were independently associated with CA. Patients with hyponatremia (sodium level ≤134 mEq/L) had 3.050-fold higher risk for CA than patients with normal sodium level (odds ratio: 3.050, 95% confidence interval: 1.668-5.576). The results of the ROC analysis performed to assess the role of sodium level in detecting CA showed a sensitivity of 27.8% and a specificity of 92.1% (cut-off: 133.5 meq/L) (p = 0.001; area under the curve: 0.612 [0.539-0.684]).

CONCLUSIONS: Clinicians should be aware of the higher likelihood of CA occurrence in patients with appendicitis in whom hyponatremia, leukocytosis, or lymphopenia is detected in the laboratory examination.

Key Words:
Complicated appendicitis, Hyponatremia, Inflammatory response.

Introduction

Acute appendicitis, defined as the inflammatory disease of the appendix, is among the most common causes of "acute abdomen" and is the leading cause of urgent abdominal surgery[1]. Appendicitis often occurs in the second and third decades of life. The incidence of appendicitis is the highest in individuals aged 10-19 years and the lowest in children aged <9 years. The male-to-female ratio is reported to be 1.4:1[2], and the lifetime incidence of appendicitis ranges from 7% to 8%[3].

Acute appendicitis is mainly divided into two types, as complicated acute appendicitis (CA) and uncomplicated acute appendicitis (UCA). CA can be accompanied by gangrenous appendicitis, perforated appendix, phlegmon, or abscess in the appendix[4]. Surgical site infection is reported in 3.3%–10.3% of the cases after appendectomy, while intraabdominal abscess is reported in 9.4%. Mortality rates in developing countries range between 1-4%, while developed countries report values below 1%[3]. Perforated appendicitis occurs in 29 per 100,000 patients[5], and it is more common in men than in women[2]. Despite the decrease in the incidence of acute appendicitis, CA incidence is increasing[6]. The degree of inflammation is exacerbated in CA compared to UCA. Therefore, various inflammatory markers, such as C-reactive protein (CRP), leukocyte count, neutrophil count, and erythrocyte sedimentation rate, have been examined to predict CA[7]. Inflammation causes an increase in the plasma levels of interleukin (IL)-1b and IL-6, which stimulate antidiuretic hormone (ADH) release, ultimately causing hyponatremia[8-10]. Possible relationships

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between severe inflammation and sodium levels are reported in appendicitis, and some studies have suggested that the decrease in sodium level may be more profound in CA due to increased severity of inflammation[11-14].

Early prediction of CA in in patients with acute appendicitis can provide clinicians with the chance to plan appropriate interventions. In this study, we aimed to determine the predictive value of some inflammatory cells and hyponatremia in differentiating UCA from CA.

Patients and Methods

This retrospective cohort study was conducted by examining data of patients who underwent an urgent appendectomy in Department of General Surgery, Eskisehir Osmangazi University from January 01, 2016 to January 01, 2021. Ethical approval was obtained from the Non-Invasive Clinical Research Ethics Committee of Eskişehir Osmangazi University, Turkey (date: 12.01.2021, decision no: 09).

Study Group

All patients who underwent urgent appendectomy with the diagnosis of acute appendicitis between the relevant dates were assessed for inclusion into the study (n = 772). Patients who had elective surgeries and diseases that may affect sodium levels, such as diabetes insipidus and renal failure, were excluded from the study. Also, subjects who had undergone appendectomy for other reasons (malignancy etc.) and patients who underwent appendectomy but were not diagnosed with appendicitis, as determined by pathological examination, were excluded from the study. Therefore, the analyses only included patients with findings showing appendiceal inflammation in the pathological examination of specimens obtained from appendectomy operations.

Measurements

Abdominal USG was performed in all patients before the operation, and pelvic CT with intravenous contrast was performed as a complementary examination in 113 cases. Contrast-enhanced pelvic MRI was performed in 3 cases as a complementary examination. Afterwards, surgical procedures were performed. The surgical and pathology reports of the patients were reviewed retrospectively from the hospital registry system. The parameters collected for this study were as follows:

- Characteristics of the patients (age and gender);
- Surgery type (open or laparoscopy);
- Type of acute appendicitis (complicated or uncomplicated);
- Preoperative laboratory findings (sodium level, leukocyte count, neutrophil count, and lymphocyte count) up to 24 h before the surgery.

Patients with perforation or phlegmon in the pathological examination and patients with intraabdominal abscess or peritonitis in the surgical report were diagnosed with CA. Patients were divided into two groups according to the clinical type of appendicitis, the UCA and CA groups. A serum sodium level of ≤134 meq/L was accepted as the threshold to define hyponatremia.

Statistical Analysis

All analyses were performed on SPSS v21 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used for the normality check. According to the normality of distribution, data are given as median (1st quartile–3rd quartile) for continuous variables and as frequency (percentage) for categorical variables. Nonnormally distributed variables were analyzed with the Mann–Whitney U test. The chi-square test or Fisher's exact test was used to compare groups of categorical variables. Multiple logistic regression analysis (forward conditional method) was performed to determine factors independently associated with CA. The diagnostic performance of the variables was assessed by using the receiver operating characteristic (ROC) curve analysis, and $p < 0.05$ values were accepted as significant results.

Results

In this study, 10.2% (n = 79) of 772 acute appendicitis cases were CA. Mean age (33 *vs.* 40 years, $p = 0.001$) and male patient frequency (48.8% *vs.* 63.3%, $p = 0.014$) were significantly higher in the CA group than in the UCA group. Patients in the CA group were more frequently treated laparoscopically, whereas those in the UCA group were more frequently treated with open surgery ($p = 0.004$). The leukocyte and neutrophil counts were significantly higher ($p = 0.002$ and $p = 0.001$, respectively), while lymphocyte count was lower ($p < 0.001$) in the UCA group than in the CA group. While the frequency

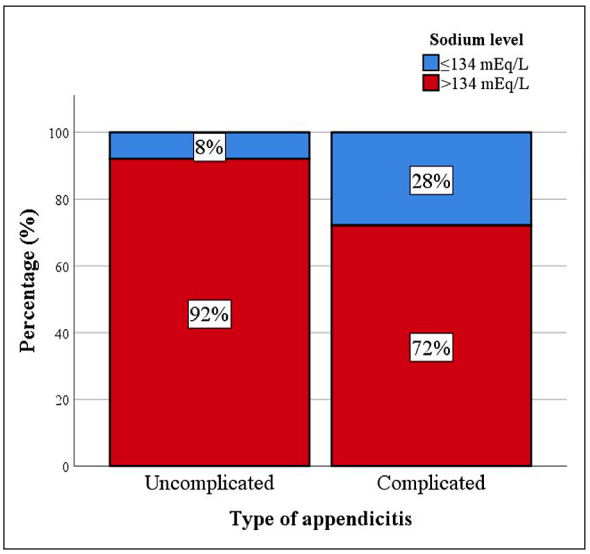

Figure 1. Sodium level according to the type of appendicitis.

of hyponatremia was 7.9% in the UCA group, it was 27.8% in the CA group ($p < 0.001$) (Figure 1). The summary of patient characteristics and clinical features according to the type of appendicitis are shown in Table I.

The results of the ROC analysis, which was performed to determine the role of sodium level in detecting CA, revealed a sensitivity of 27.8% and specificity of 92.1% at a cutoff of 133.5 meq/L ($p = 0.001$; area under the curve, 0.612 [95% confidence interval, 0.539-0.684]) (Figure 2).

Multiple logistic regression analysis revealed that high age ($p = 0.001$), male sex ($p = 0.014$), high leukocyte count ($p = 0.045$), low lymphocyte count ($p = 0.023$) and hyponatremia ($p<0.001$) were risk factors that were independently associated with CA. Patients with hyponatremia (sodium level ≤134 mEq/L) had 3.050-fold higher likelihood to have CA than patients with normal sodium level (odds ratio: 3.050, 95% confidence interval: 1.668-5.576) (Table II). Other variables included in the analysis, surgery type ($p = 0.051$) and neutrophil count ($p = 0.313$) were found to be non-significant.

Discussion

Acute appendicitis is the leading cause of acute abdomen that requires urgent intervention. If the severity of the clinical picture can be predicted before the planned surgery, preparations can be made against possible undesirable events. Therefore, distinguishing CA from UCA will allow clinicians to plan the intervention and take measures against possible problems that may be encountered during surgery. This study attempted to differentiate UCA from CA cases based on some clinical features, especially sodium level; results showed that the frequency of hyponatremia was higher in the CA group than in the UCA group. Leukocyte counts were significantly higher and lymphocyte levels were lower in the CA group than in the UCA group. In addition, the CA group consisted of relatively older patients, with a predominance of men.

Many previous studies[15,16] have shown that serum sodium level is associated with mortali-

Table I. Summary of patients' characteristics and clinical features according to the type of appendicitis.

	Type of appendicitis		
	Uncomplicated (n = 693)	Complicated (n = 79)	p
Age (year)	33 (25-45)	40 (27-68)	0.001
Sex			0.014
Female	355 (51.2%)	29 (36.7%)	
Male	338 (48.8%)	50 (63.3%)	
Surgery type			0.004
Open	400 (57.7%)	59 (74.7%)	
Laparoscopy	293 (42.3%)	20 (25.3%)	
Leukocytes (10^3/µl)	12.71 (9.98-15.90)	14.50 (11.40-18.00)	0.002
Neutrophil (10^3/µl)	9.80 (6.90-13.10)	11.30 (8.60-15.40)	0.001
Lymphocyte (10^3/µl)	1.81 (1.31-2.50)	1.50 (1.00-2.10)	< 0.001
Sodium level			< 0.001
≤ 134 mEq/L	55 (7.9%)	22 (27.8%)	
> 134 mEq/l	638 (92.1%)	57 (72.2%)	

Data are given as median (1st quartile-3rd quartile) for continuous variables and as frequency (percentage) for categorical variables.

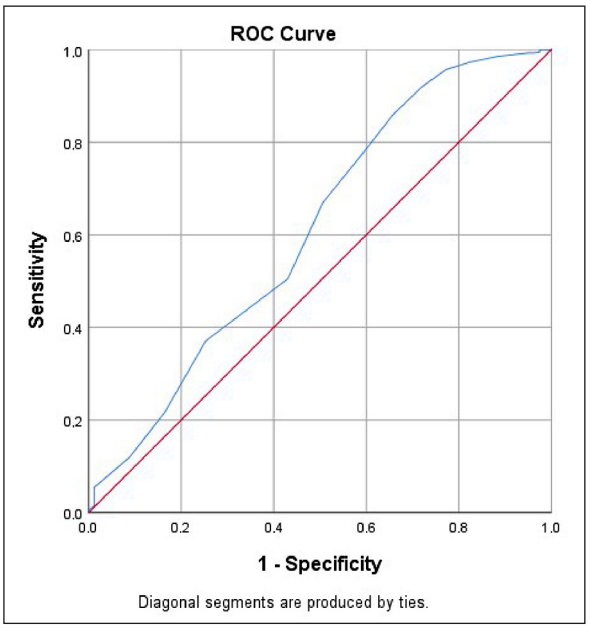

Figure 2. ROC analysis demonstrating the ability of serum sodium levels to predict complicated appendicitis.

ty and morbidity in ischemic events occurring in the gastrointestinal tract. Serum sodium level has also been associated with complications and mortality after gastrointestinal surgeries[9]. In addition, our literature review revealed various studies[11-14,17,18] with the existence of a relationship between the development of complications in acute appendicitis and serum sodium level. In a systematic review[17] focusing on the role of hyponatremia in identifying CA, the authors emphasized that serum sodium level can be a useful biomarker to detect CA. In another recent systematic review and meta-analysis[19], the authors also reported that hyponatremia was a useful parameter to distinguish CA cases from UCA cases. Other studies[11-14,18,20] have comprehensively demonstrated the relationship between complicated appendicitis and lower sodium level in pediatric and adult populations. In recent studies[21,22], it was noted that the preoperative sodium value had an acceptable level of discrimination in predicting CA at a cut-off point of ≤134 mEq/L. The present study showed that hyponatremia was an independent risk factor associated with CA, and that sodium level (≤133.5 mEq/L) could be utilized to detect UCA, consistent with the results of previous studies. Although the relationship between hyponatremia and CA has been shown in previous studies[19], the underlying reason for this relationship has not been clearly revealed. This relationship was thought to be explained by the hypothesis that the severity of inflammation is associated with the release of ADH. According to this hypothesis, increased levels of ILs in diseases that cause relatively severe inflammation are suggested to stimulate ADH release. Increasing ADH levels cause dilutional hyponatremia by reducing the excretion of water from the renal tubular system[8-10].

Given the retrospective design of this study, a cause-effect relationship could not be demonstrated. Nevertheless, the results of this study and those of related studies reveal that serum sodium level is a potential marker that has value in predicting CA cases, especially since it is an inexpensive, widely used, and accessible laboratory parameter.

The variable characteristics of patients based on sex and age can affect the incidence and clinical course of various diseases. Many studies[13,14,23-25] have reported that age and sex, similar to sodium level, can be independent parameters of predicting CA. In one study[23], researchers showed that older age increases the incidence of complicated appendicitis by 3% per year, while being male increases it by 1.9-fold. In many related studies[13,14,24,25], the frequency of

Table II. Significant factors independently associated with complicated appendicitis, multiple logistic regression analysis.

	β coefficient	Standard error	*p*	Exp (β)	95.0% CI for Exp (β)	
Age	0.025	0.007	0.001	1.025	1.011	1.040
Sex, male	0.631	0.256	0.014	1.879	1.136	3.106
Leukocytes	0.038	0.019	0.045	1.038	1.001	1.077
Lymphocyte	-0.386	0.170	0.023	0.680	0.488	0.948
Sodium level, ≤ 134 mEq/L	1.115	0.308	< 0.001	3.050	1.668	5.576
Constant	-3.585	0.579	< 0.001	0.028		

CI: Confidence Interval, Nagelkerke R^2=0.140.

CA is found to be increased in males and older patients. By contrast, some rare studies[11,26] have revealed that age and sex are associated with higher incidence of both CA and UCA; thus, they suggest no apparent relationship between these factors and increased likelihood of CA. In the present study, the number of male patients was higher in the CA group and patients with CA were older. Considering that the majority of the literature is in agreement with these results, we believe that clinicians should be aware that higher age and male sex are primary factors when assessing the likelihood of CA.

Acute appendicitis progresses with inflammation. Therefore, as in other inflammatory diseases, the increase in the levels of acute-phase reactants and inflammatory cells was not surprising. Undoubtedly, other conditions such as complications that exacerbate inflammation will increase, to some extent, the level of these biomarkers. Similarly, the CA *vs.* UCA comparisons of the current study revealed that leukocyte and neutrophil counts increased relatively more in subjects with CA. The results of previous studies are also compatible with these findings. Numerous studies have indicated that leukocytes and CRP are associated with complicated appendicitis, and the extent of leukocyte count increase has been extensively investigated in previous studies. Although a high leukocyte count can predict the probability of CA at a certain accuracy, leukocyte increase alone is not valuable because it is not specific to the appendix, since it increases in many other diseases[27]. Similar studies[11,28] have reported that the increase in leukocyte and neutrophil counts was associated with the severity of inflammation of the appendix and the development of CA. Nonetheless, some researchers[25,26,29-31] suggest that leukocyte or neutrophil count alone may be valuable in differentiating UCA from CA. However, generally it is accepted that leukocyte count can be used to support the diagnosis of acute appendicitis, but it is not valuable in differentiating UCA from CA[32]. Although the increase in inflammatory cells appears to be associated with the clinical severity of UCA and CA, these parameters are highly nonspecific.

The retrospective design of the study is an important limitation. Therefore, different parameters that could be valuable in estimating CA were not examined, and a cause–effect relationship could not be established. The single-center setting, relatively low number of complicated cases, and varying measurement times limit the generalizability of the results. In addition, other hormonal and clinical parameters that may affect laboratory parameters have not been evaluated. These variables may have influenced the results and comparisons between groups.

Conclusions

CA can be distinguished from UCA based on some clinical features. The results of this study indicate that older patients and male patients with acute appendicitis have a higher risk of developing CA. Clinicians should also be aware of the higher likelihood of CA in patients with hyponatremia, leukocytosis, or lymphopenia. In future prospective studies, our results can be validated by evaluating the predictive values of these parameters for CA in larger case groups. In addition, more precise estimates can be obtained by using scoring systems created with various combinations of these parameters and could aid in the differentiation of CA from UCA.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Committee Approval

This study was approved by the Non-Invasive Clinical Research Ethics Committee of Eskisehir Osmangazi University University (Decision no. 09, dated 12.01.2021).

Informed Consent

All patients included in this study had signed an informed consent form.

Authors' Contribution

Concept: D.B.O.; Design: D.B.O., A.K.; Supervision: D.B.O., A.K.; Materials: A.K.; Data: D.B.O., A.K.; Analysis: D.B.O., A.K.; Literature search: D.B.O.; Writing: D.B.O., A.K., H.D.; Critical revision: H.D., B.U.

Financial Disclosure

The authors declared that this study has received no financial support.

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