



## The value of ischemia-modified albumin and oxidative stress markers in the diagnosis of acute appendicitis in adults

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### ARTICLE INFO

#### Article history:

Received 26 September 2018

Received in revised form 14 February 2019

Accepted 7 March 2019

#### Keywords:

Acute appendicitis

Ischemia-modified albumin

Oxidative stress markers

### ABSTRACT

**Introduction:** The present study evaluates the predictive value of such markers as ischemia-modified albumin (IMA), malondialdehyde (MDA) and glutathione peroxide (GSH-Px), in addition to parameters associated with inflammation, oxidative stress and ischemia, playing roles in the pathology of acute appendicitis (AA), including c-reactive protein (CRP), procalcitonin (PCT) and complete blood count (CBC) parameters and their ratios, for the diagnosis of AA in adults.

**Material and methods:** The study included 51 patients with histologically confirmed appendicitis and 45 healthy controls who referred to the emergency care unit between January and June 2018. The appendicitis cases were classified into two groups, as complicated and non-complicated, based on postoperative pathological investigations.

**Results:** Of all the appendicitis cases, 68.5% (n = 35) were non-complicated and 31.4% (n = 16) were complicated. IMA (positive LR = 3.0, negative LR = 0.1), GSH-Px (positive LR = 0.5, negative LR = 1.8), MDA (positive LR = 1.8, negative LR = 0.6), CRP (positive LR = 7.2, negative LR = 0.2), PCT (positive LR = 0.7, negative LR = 1.3), WBC (positive LR = 2.9, negative LR = 0.3), neutrophil-lymphocyte ratio (positive LR = 3.2, negative LR = 0.1) thrombocyte lymphocyte ratio (positive LR = 1.6, negative LR = 0.5) and IMA/albumin ratio (positive LR = 3.3, negative LR = 0.1) levels in the appendicitis cases were evaluated by a characteristic receiver operating characteristic (ROC) curve. In addition, IMA levels were significantly higher in the complicated cases (0.40 ± 0.05 AbsU) than in the non-complicated cases (0.29 ± 0.04 AbsU) (p < 0.0001).

**Conclusion:** Our results showed that IMA (negative LR = 0.1), CRP (positive LR = 7.2, negative LR = 0.2), NLR (negative LR = 0.1) and IMA/albumin ratio (negative LR = 0.1) can serve as important diagnostic biomarkers for AA patients. We therefore believe that before clinically confirming an AA diagnosis, these parameters may be used as diagnostic tools in addition to CBC parameters, CRP levels and radiological imaging studies.

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### 1. Introduction

Despite the mortality and morbidity associated with acute appendicitis (AA), its prevalence has been decreasing in recent years, although a differential diagnosis of AA is still challenging, and it still represents one of the most important causes of acute abdomen. While a diagnosis of AA is based essentially on clinical symptoms, physical

examination findings and medical history, radiological methods, particularly ultrasonography and computerized tomography, are also commonly used in its diagnosis [1,2]. Problems such as the unavailability of such imaging devices in every hospital and the absence of experienced radiologists can be listed as obstacles to diagnosis, and these practical limitations direct clinicians to focus on serological investigations.

Mucosal ulceration in the muscularis propria due to a luminal obstruction and bacterial invasion are known to be early events underlying an AA pathogenesis. In such cases, increased luminal pressure due to enhanced secretions causes mucosal ischemia. It is therefore

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believed that, in addition to inflammatory processes, oxidative stress status and ischemia are also involved in the pathology and progression of AA [3–5]. Regardless of this, clinicians still focus mostly on systemic inflammation markers for an AA diagnosis, and accordingly, recent studies have focused on markers such as neutrophil-lymphocyte ratio (NLR), thrombocyte lymphocyte ratio (PLR), mean platelet volume (MPV), c-reactive protein (CRP) and procalcitonin (PCT), which are in common use and have demonstrated diagnostic benefits [6–10]. Ischemia assessment is not included in the current scoring systems, and so we believe that ischemia has not been sufficiently addressed in this context.

Free radical reactions play a significant role in biological systems, and produced radicals mostly originate from oxygen. Due to their unstable nature, active oxygen species interact with and damage all cellular components, and mainly lipids, proteins and nucleic acids. Malondialdehyde (MDA) is a product of lipid peroxidation that is induced by free radicals, and has a strong defense system, known as an antioxidant system, which protects the organism from the harmful effects of free radicals. Glutathione peroxidase (GSH-Px) is an important antioxidant enzyme that prevents the harmful effects of free radicals by metabolizing them enzymatically. However, under certain conditions, the defense system may lack sufficiency, leading to the development of oxidative stress [11,12].

Ischemia-modified albumin (IMA) is a biological marker that is produced as a result of the modification of albumin by reactive oxygen radicals, and its levels can be measured by colorimetric methods through the addition of cobalt to patient serum [13]. IMA levels increase in the presence of ischemia-based conditions such as stroke, acute mesentery ischemia and acute coronary syndrome [14–16].

The present study evaluates the predictive value of such markers as IMA, MDA and GSH-Px, in addition to parameters associated with inflammation, oxidative stress and ischemia, playing roles in the pathology of AA, including CRP, PCT and complete blood count (CBC) parameters and their ratios, for the diagnosis of AA in adults.

## 2. Material and methods

A total of 96 cases, including 51 patients who referred to the emergency unit of our hospital between January 2018 and June 2018 and who were diagnosed with appendicitis based on pathological investigations, and age- and gender-matched 45 healthy controls, were enrolled in the study. The study was approved by local ethics committee (Session: 2017/20, Decision No: 12). All patients were aged 18 years and above, had no concomitant disease, had received a clinical diagnosis of AA and had undergone surgery, after which the diagnosis of appendicitis was confirmed pathologically. The participants were informed about the study and all provided written informed consent for participation.

In patients whose physical examination suggested AA after referring to the emergency unit, the diagnosis of AA was confirmed through routine procedures including CRP, PCT and CBC analyses and imaging investigations. For a CBC analysis by phlebotomy, 5 cm<sup>3</sup> blood samples were obtained from the participants and placed into EDTA-containing purple-capped tubes. For CRP, PCT, IMA, MDA and GSH-Px analyses, an 8 cm<sup>3</sup> venous blood sample was obtained from the participants and placed into non-anticoagulated yellow-capped blood collection tubes. After the clotting of the blood samples collected in the yellow-capped tubes, the serum was separated through centrifugation at 4000 rpm for 10 min. Routine analyses were performed on the obtained serum samples, which were then stored at (–) 80 °C until the time of analysis for IMA, MDA and GSH-Px. Serum IMA levels were measured colorimetrically in accordance with the method developed by Bar et al. [17], and serum total MDA levels were measured spectrophotometrically based on the method described by Okhawa et al. [18]. The Beutler method was used to measure GSH-Px activity [19]. CBC was analyzed using a Sysmex XT-1800i automatic hematology device (Sysmex, Kobe, Japan). The PCT analysis was performed using a Getein 1600 Immuno fluorescence Quantitative Analyzer (GeTeinBioMedical Inc.,

Portland, USA) device. CRP levels were determined via the nephelometric method (Dade Behring BN2 Nephelometer Analyzer, DADE Behring, USA). The pathology results of patients who underwent surgery with a diagnosis of AA were reviewed, and based on these reviews, the patients were divided into two groups, as having non-complicated or complicated appendicitis. The non-complicated group included cases of AA, obliterated appendicitis and lymphoid hyperplasia; while the complicated group included cases of perforated appendicitis, acute phlegmonous and acute gangrenous appendicitis.

### 2.1. Statistical analysis

The statistical analyses of the data collected in this study were performed using the SPSS 22.0 software package (SPSS Inc., Chicago, Illinois, USA). Continuous data was expressed as means and standard deviations (SD), while categorical data was presented as numbers and percentages. Continuous variables were compared between independent groups using a Student's *t*-test. For between-group comparisons, a Chi-squared ( $\chi^2$ ) test was used to evaluate the categorical variables between two groups. Receiver operating characteristic (ROC) curves were used to assess the power of markers in the prediction of appendicitis. Based on this method, the essential criteria for the best test description were considered to have a sensitivity of 100%, a zero false positive rate (1-Specificity = 0), an area under the curve (AUC) value of 1 and a diagnostic AUC value of  $p < 0.05$ . In order to assign cut-off values, the Youden index that reflected the highest total value of sensitivity and specificity, corresponding to the closest point to left upper corner of the ROC curve, was used. Sensitivity and specificity values were estimated within a 95% confidence interval to evaluate the accuracy of the diagnostic tests, and results were tabulated. Also likelihood ratios (LRs) were calculated by standard formulas: positive LR = sensitivity / (1 – specificity) and negative LR = (1 – sensitivity) / specificity. It is considered LR+ to be helpful if  $\geq 5$  and LR– if  $\leq 0.2$ . A *p* value of  $< 0.05$  was considered statistically significant.

## 3. Results

A total of 96 cases were entered into the study, including 51 (53%) patients with appendicitis and 45 (47%) healthy controls. When gender distribution was evaluated within the groups, men and women constituted 57% ( $n = 29$ ) and 43% ( $n = 22$ ) percent of the appendicitis group, and 64% ( $n = 29$ ) and 36% ( $n = 16$ ) percent of the control group, respectively. Gender distribution was not significantly different between the two groups ( $\chi^2$ ,  $p = 0.448$ ). The mean ages in the appendicitis group and the control group were  $33.6 \pm 16.2$  years (min–max 18–84 years) and  $30.9 \pm 12.3$  years (min–max 19–63 years), respectively. The age distribution was not significantly different between the two groups ( $p = 0.358$ ).

Of all the appendicitis cases, 69% ( $n = 35$ ) were non-complicated and 31% ( $n = 16$ ) were complicated. The mean age of the patients with non-complicated and complicated appendicitis was  $34.1 \pm 14.3$  years (min–max 18–70 years) and  $32.7 \pm 20.2$  years (min–max 18–84 years), respectively.

Table 1 shows the mean GSH-Px, MDA, IMA, WBC, CRP, PCT, platelet count, MPV, NLR, PLR, Albumin and IMA/Albumin values in the appendicitis and control groups. IMA, WBC, CRP, NLR, PLR, and IMA/Albumin values were significantly higher in the appendicitis group than the control group (*p* values respectively;  $< 0.001$ ,  $< 0.001$ ,  $< 0.001$ ,  $< 0.001$ ,  $< 0.001$ ,  $< 0.001$ ). However, GSH-Px, MPV and Albumin values were significantly lower in the group with appendicitis than the control group (*p* values respectively; 0.001, 0.018,  $< 0.001$ ). It was found that there was no difference between the groups in the other tests.

Table 2 presents the cut-off, positive LR, negative LR, AUC, 95% confidence interval and *p* values for the power of the GSH-Px, IMA, WBC, CRP, PCT, NLR, PLR, Albumin and IMA/Albumin parameters in the prediction of AA. It was detected that the only useful positive test is CRP (positive LR = 7.2) and the only useful negative tests are IMA with a negative LR = 0.1, the NLR with a negative LR = 0.1 and IMA/Albumin

**Table 1**

GSH-Px, MDA, IMA, WBC, CRP, PCT, platelet count, MPV, NLR, PLR, Albumin and IMA/Albumin values in appendicitis and control groups.

	Appendicitis (n:51) Mean ± SD	Control (n:45) Mean ± SD	p <sup>a</sup>
GSH-Px (nmol/ml)	81.8 ± 46.4	153.2 ± 136.2	0.001
MDA (nmol/ml)	9.4 ± 4.0	8.1 ± 4.1	0.107
IMA (AbsU)	0.33 ± 0.1	0.21 ± 0.1	<0.001
WBC (10 <sup>3</sup> /μL)	12.4 ± 4.5	7.7 ± 2.1	<0.001
CRP (mg/dL)	31.2 ± 39.9	3.7 ± 1.6	<0.001
PCT (ng/mL)	0.5 ± 2.8	0.01 ± 0.02	0.276
Platelet (10 <sup>3</sup> /μL)	259 ± 61.7	256.7 ± 47.9	0.841
MPV (fL)	9.6 ± 2.2	10.4 ± 0.9	0.018
NLR	6.7 ± 7.7	2.0 ± 0.7	<0.001
PLR	158.2 ± 74.8	113.6 ± 29.5	<0.001
Albumin (g/dL)	4.3 ± 0.4	4.6 ± 0.3	<0.001
IMA/Albumin	0.08 ± 0.02	0.05 ± 0.02	<0.001

GSH-Px: glutathione peroxide, MDA: malondialdehyde, IMA: ischemia-modified albumin, WBC: white blood count, CRP: c-reactive protein, PCT: procalcitonin, MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio, PLR: platelet lymphocyte ratio, SD: standard deviation.

<sup>a</sup> Groups were compared using the Student's *t*-test.

**Table 2**

Cut-off, positive LR, negative LR, AUC, 95% confidence interval and p values for the power of GSH-Px, IMA, WBC, CRP, PCT, NLR, PLR, Albumin and IMA/Albumin parameters in the prediction of AA.

	Cut-off	Positive LR	Negative LR	AUC	95% CI	p <sup>a</sup>
GSH-Px (nmol/ml)	90.5	0.5	1.8	0.261	16.1–36.0	<0.001
MDA (nmol/ml)	7.6	1.8	0.6	0.624	51.1–73.7	0.037
IMA (AbsU)	0.26	3.0	0.1	0.863	78.9–93.7	<0.001
WBC (10 <sup>3</sup> /μL)	8.44	2.9	0.3	0.836	75.7–91.5	<0.001
CRP (mg/dL)	3.98	7.2	0.2	0.836	74.5–92.6	<0.001
PCT (ng/mL)	0.05	0.7	1.3	0.627	51.6–73.8	0.032
NLR	2.25	3.2	0.1	0.908	84.7–96.9	<0.001
PLR	114.2	1.6	0.5	0.689	58.3–79.5	0.001
Albumin (g/dL)	4.5	0.5	2.0	0.293	18.8–39.8	<0.001
IMA/Albumin	0.06	3.3	0.1	0.888	82.3–95.3	<0.001

AUC: area under curve, CI: confidence interval, LR: likelihood ratios, GSH-Px: glutathione peroxide, MDA: malondialdehyde, IMA: ischemia-modified albumin, WBC: white blood count, CRP: c-reactive protein, PCT: procalcitonin, NLR: neutrophil to lymphocyte ratio, PLR: platelet lymphocyte ratio.

<sup>a</sup> Values in groups were calculated using the ROC curve.

with a negative LR = 0.1. None of the other tests are useful in ruling in or ruling out appendicitis.

As the mean platelet count was not significantly different between the two groups, this parameter was excluded from the analysis for the prediction of appendicitis.

Table 3 presents GSH-Px, MDA, IMA, WBC, CRP, PCT, NLR, and PLR values for complicated and non-complicated cases. IMA values was found useful test for the complicated appendicitis group.

ROC curves for inflammatory markers are presented in Fig. 1.

#### 4. Discussion

Acute appendicitis is still one of the most frequently seen causes of acute abdomen, and appendectomy is conventionally considered as the optimum method in the treatment of AA [20]. The fact that ultrasonography and computerized tomography, as the radiological methods used for the diagnosis of AA and its complications, are not available in every hospital, and there are limitations in the experience of radiologists in achieving definitive conclusions, result in challenges in the diagnosis of AA, and clinicians tend to focus, therefore, on finding certain serological markers. The main markers evaluated in several studies in terms of their diagnostic value for AA include WBC, NLR, PLT, PLR, MPV, CRP and PCT [6,8,9,21–23]. Compared to the number of studies evaluating inflammatory markers, there are only a limited number of studies

**Table 3**

GSH-Px, IMA, WBC, CRP, PCT, NLR, and PLR values for complicated and non-complicated cases.

	Complicated (n = 16) Mean ± SD	Non-complicated (n = 35) Mean ± SD	p <sup>a</sup>
GSH-Px (nmol/ml)	84.7 ± 48.5	80.5 ± 46.1	0.770
MDA (nmol/ml)	10.1 ± 4.6	9.2 ± 3.8	0.454
IMA (AbsU)	0.40 ± 0.05	0.29 ± 0.04	0.000
WBC (10 <sup>3</sup> /μL)	12.2 ± 4.7	12.4 ± 4.5	0.878
CRP (mg/dL)	43.8 ± 52.2	25.4 ± 32.1	0.206
PCT (ng/mL)	1.3 ± 5.0	0.1 ± 0.3	0.357
NLR	8.2 ± 12.5	6.0 ± 4.1	0.487
PLR	160.0 ± 93.7	157.4 ± 66.0	0.910

GSH-Px: glutathione peroxide, MDA: malondialdehyde, IMA: ischemia-modified albumin, WBC: white blood count, CRP: c-reactive protein, PCT: procalcitonin, NLR: neutrophil to lymphocyte ratio, PLR: platelet lymphocyte ratio, SD: standard deviation.

<sup>a</sup> Groups were compared using the Student's *t*-test.

assessing the diagnostic value of ischemic and oxidative stress-related markers, considering that luminal obstruction, mucosal ulceration and the development of ischemia play particular roles in the pathophysiology of AA [24].

Male patients constituted 67% of the population in a study investigating the role of NLR in the diagnosis of AA in 1067 patients operated on for AA [9], and 59% of the population in another study investigating the value of MPV, NLR, PLT and bilirubin levels in 3392 patients with simple or perforated appendicitis [25]. In the present study, 57% of the patients with AA were male, supporting the previous findings in the literature. Previous studies have also reported an overall mean age of 30 years among the adult patients with AA, which is again consistent with the mean age of the patient population in the present study [1,21,25].

There have been several studies in literature investigating the predictive value of inflammatory parameters in the diagnosis of AA. Among those, the most common are CBC parameters (WBC, NLR, PLT, MPV, PLR), CRP and PCT [8–10,23]. In a study by Sahbaz et al. evaluating leukocyte count and neutrophil percentage in the prediction of non-complicated and complicated appendicitis, predictive neutrophil ratio was found to be of higher sensitivity and specificity for AA, while an increased leukocyte count was implicated as a risk factor for complicated appendicitis [6]. In a study evaluating basic laboratory parameters in AA cases, the cut off-values for WBC 11.900/mm<sup>3</sup> (positive LR = 2.2, negative LR = 0.4), and for NLR 3.0 (positive LR = 1.7, negative LR = 0.4) were reported [25]. In the study by Kahraman et al., NLR levels of 8.10 ± 7.0 in the appendicitis group and 5.89 ± 5.2 in the control group were reported, and the difference between two groups was found to be statistically significant (*p* < 0.001). ROC curves constructed to assess the power of NLR in the prediction of appendicitis showed a cut-off value of 4.68, AUC of 0.639 (*p* < 0.001), (positive LR = 4.2, negative LR = 0.4) [9].

Studies performed to evaluate MPV levels in appendicitis patients reported conflicting results. In a recent study performed in Turkey, the mean MPV values in appendicitis patients and the control group were reported to be 9.3 ± 8 fL and 8.5 ± 0.9 fL (*p* = 0.0005), respectively, and the authors underlined that the elevated MPV values could help in a clinical diagnosis in terms of determining the severity of the disease [26]. Another study showed that MPV was not a useful parameter in the diagnosis of AA [25]. A previous meta-analysis, on the other hand, showed that AA patients had lower MPV values when compared to the healthy individuals, and the decrease was found to be significant in terms of diagnosis (*p* = 0.037) [27]. While there are a limited number of studies investigating PLR in literature, in a study performed by Nazik et al. addressing the role of IMA and other inflammatory markers in the diagnosis of pediatric appendicitis, PLR levels were found to be significantly higher in the patients with appendicitis when compared to the control group (*p* = 0.001) [28]. In the present study, the WBC, NLR and PLR levels of patients with AA were significantly higher than those of the control group (*p* < 0.001), and this finding was in compatible

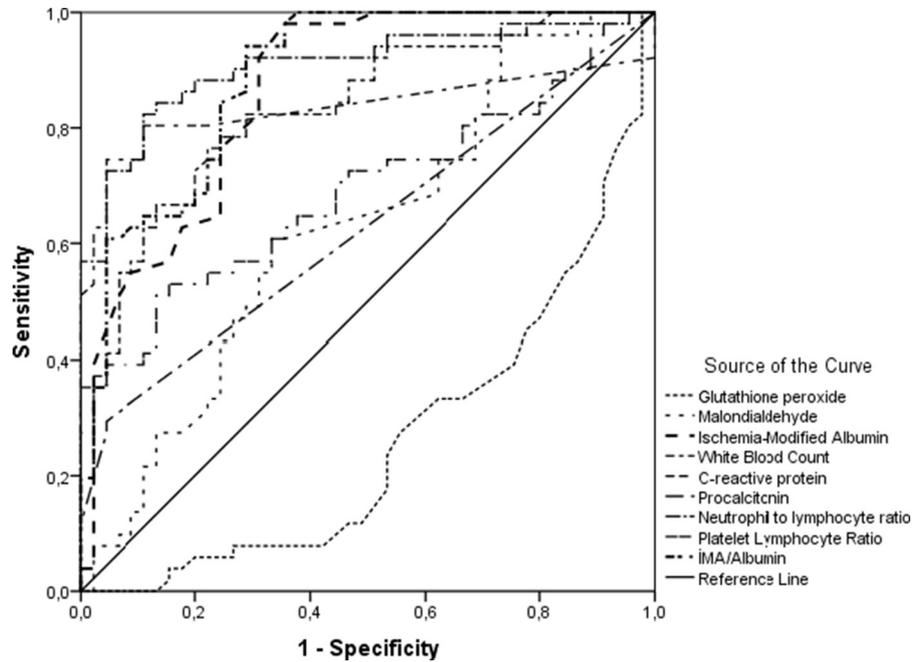


Fig. 1. ROC curves for inflammatory markers.

with the literature. Moreover, MPV levels were found to be significantly lower in the AA group than in the control group in the present study ( $p = 0.018$ ). On the other hand, PLT levels were not significantly different between the appendicitis patients and the controls, and this finding was consistent with literature ( $p = 0.841$ ).

In a study evaluating CRP levels in AA and investigating its relation with inflammation of the appendix, CRP levels were shown to be significantly increased in the presence of an inflamed appendicitis [29]. In a meta-analysis that reviewed systematically the diagnostic accuracy of PCT, CRP and WBC in non-complicated and complicated appendicitis, the ROC curve analyses indicated that CRP (positive LR = 4.5, negative LR = 0.5), WBC (positive LR = 2.5, negative LR = 0.5) and PCT (positive LR = 3.0, negative LR = 0.8) [23]. In another study, PCT value (positive LR = 3.1, negative LR = 0.8) was determined in AA patients who were admitted to emergency department [30]. In line with previous studies, the appendicitis patients in the present study recorded significantly higher CRP levels than the control group ( $p < 0.001$ ), while PCT was not significantly different between the two groups ( $p = 0.276$ ).

IMA is a marker that is produced after the modification of albumin by reactive oxygen radicals, and its levels to date have been investigated in several studies, including those analyzing patients with strokes, acute mesenteric ischemia, acute coronary syndrome and alopecia [14–16,31]. There are a few studies in literature that also investigated IMA levels in AA patients. In a study of pediatric patients with appendicitis, preoperative IMA values in the patient and control groups were found to be  $0.56 \pm 0.1$  AbsU and  $0.33 \pm 0.1$  AbsU, respectively, indicating that patients with appendicitis had significantly higher IMA levels than the controls ( $p < 0.0001$ ) [28]. Another study evaluating oxidative stress markers in adult patients with AA reported a preoperative IMA level of  $0.64 \pm 0.09$  AbsU in appendicitis patients and  $0.31 \pm 0.09$  AbsU in the controls. The IMA levels were determined to be significantly higher in the appendicitis group ( $p < 0.001$ ) [24]. In a study by Kılıç et al., the IMA levels were found to be significantly higher in the complicated appendicitis group than in the non-complicated appendicitis group ( $p = 0.012$ ) [32]. Similarly, in the present study, IMA was significantly elevated in patients with AA when compared to the healthy controls, and was superior to the other inflammatory markers in terms of predicting AA. Additionally, in the AA group, IMA was significantly higher in patients with a complicated appendicitis than in those with non-complicated appendicitis ( $p < 0.0001$ ).

Free radical reactions play significant roles in biological systems, and a significant part of the free radical species produced by an organism originates from oxygen. MDA is a product of lipid peroxidation that is stimulated by free radicals. GSH-Px is an important antioxidant enzyme that prevents the harmful effects of free radicals by enzymatically metabolizing them. There have been some studies suggesting that GSH-Px and MDA levels may be elevated in the presence of acute ischemia, and ischemia due to luminal obstruction is the pathophysiological starting point of AA [33]. A limited number of studies in the literature have investigated MDA levels in AA, and have reported conflicting results. In a study performed by Koltuksuz et al. involving pediatric patients with AA, MDA was found to be significantly elevated in cases of acute suppurative and acute perforated appendicitis when compared to cases of acute focal appendicitis and the control group [34]. In another study, patients were classified into groups as having acute phlegmonous, gangrenous or perforated appendicitis, and negative exploration findings based on their histopathological results after appendectomy, and no significant difference was noted between these groups in terms of MDA levels [3]. In the present study, we were able to identify no significant difference between the MDA levels of AA patients and healthy controls ( $p = 0.107$ ).

In the literature, we did not find any study investigating the relationship between GSH-Px and acute appendicitis patients. The data presented here is therefore the first in literature to detail this relationship. The results of the present study have demonstrated that patients with appendicitis have significantly lower GSH-Px levels when compared to the controls ( $p = 0.001$ ).

The selection of the control group from the healthy group was the limitation of our study.

In conclusion, we found that IMA (negative LR = 0.1), CRP (positive LR = 7.2, negative LR = 0.2), NLR (negative LR = 0.1) and IMA/albumin ratio (negative LR = 0.1) were important biomarkers for the diagnosis of AA patients, whereas MDA made no significant contribution to AA diagnosis. We therefore believe that before clinically confirming AA diagnosis, these parameters may be used as diagnostic biomarkers in addition to CBC parameters, CRP levels and radiological imaging studies.

#### Conflict of interest

No conflict of interest was declared by the authors.

## Financial disclosure

The authors declared that no financial support has been received from any individual or institution in respect of the study. Conceptualization; H.H., S.N., A.R.Ş., Data curation; H.H., M.S., Ö.G., Formal analysis; S.N., Funding acquisition; Investigation; H.H., S.N. M.F.Y., Methodology; S.N., M.S. Project administration; H.H., S.N., A.R.Ş., E.C., Resources; H.H., Ö.G., E.C., M.F.Y., Software; H.H., S.N. Supervision; H. H., S.N., M.F.Y., Validation; H.H., S.N., M.F.Y. Visualization; H.H., S.N., A.R.Ş., Writing - original draft; H.H., S.N., Writing - review & editing: H.H., S.N., M.F.Y..

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Availability of data and materials

All of the data and materials are available and credible in this article.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Informed consent

Permission from cases and/or their relatives was obtained with an informed consent form.

## Ethical approval

The study was approved by the ethical committee of KSÜ Hospital (Date: 06.12.2017, session: 2017/20, decision no. 12).

## Human rights

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

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