ORIGINAL ARTICLE

The diagnostic value of serum hepcidin in acute appendicitis

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ABSTRACT

BACKGROUND: Acute appendicitis (AA) is the primary cause of acute abdomen in patients presenting to the emergency department with abdominal pain. Limited studies have explored the relationship between serum hepcidin levels and AA. This study aimed to measure serum hepcidin levels in patients undergoing surgery with a preliminary diagnosis of AA and to assess whether these levels can serve as a biochemical marker for diagnosing AA.

METHODS: This study included patients aged 18 or older who presented to the emergency department between April 2018 and May 2019 and underwent surgery with a diagnosis of AA. The cohort comprised 94 patients with surgical pathology results compatible with AA (Group A), 16 patients with results not compatible with AA (Group B), and 42 healthy controls. Serum hepcidin levels were measured from venous blood samples.

RESULTS: Mean hepcidin levels were 1750±285 pg/mL in Group A, 1349±381 pg/mL in Group B, and 1066±225 pg/mL in the control group. Statistically significant differences in serum hepcidin levels were observed between Group A and the control group ($p<0.05$).

CONCLUSION: Hepcidin levels were significantly higher in patients with AA compared to both the control group and patients with surgically confirmed non-AA pathology. Therefore, hepcidin may serve as a useful adjunct in diagnosing acute appendicitis.

Keywords: Abdominal pain; acute appendicitis; adult; inflammation; hepcidin.

INTRODUCTION

Typical clinical manifestations of acute appendicitis (AA) include pain originating in the periumbilical region and radiating to the right lower quadrant, accompanied by fever, nausea, and vomiting.[1] The definitive diagnosis of the disease relies on laboratory tests and imaging studies, alongside clinical observations.[2] Clinical and laboratory findings in patients diagnosed with AA include fever, right lower quadrant tenderness, peritoneal irritation signs, elevated white blood cell (WBC) counts, and high C-reactive protein (CRP) concentrations. However, these findings may not present in the majority of patients with suspected AA.[3] Ultrasonography (USG) and computed tomography (CT), crucial for diagnosing AA, pose challenges such as high costs, transportation difficulties, and the risk of ionizing radiation. Additionally, these auxiliary tests may not be diagnostic in the early stages of the disease, potentially leading to delays.[4,5] Given these factors, early diagnosis

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of AA is difficult, and delayed diagnosis can lead to complications such as plastron appendicitis, appendiceal perforation, peritonitis following perforation, intra-abdominal abscess, sepsis, and ileus.[6] The difficulties associated with diagnosing AA, particularly the increased morbidity and mortality resulting from delayed diagnosis, have prompted researchers to seek biomarkers that can identify AA with high sensitivity and specificity.[2,4]

Hepcidin, an antimicrobial peptide molecule consisting of 25 amino acids synthesized in the liver, primarily regulates iron homeostasis, controlling iron absorption from the intestines and iron release from macrophages.[7,8] It inhibits the release of iron from intestinal enterocytes and reticuloendothelial cells and reduces the amount of iron in circulation. This mechanism prevents iron utilization by microorganisms.[9] Hepcidin secretion is stimulated by an increased iron load and inflammation. Research has demonstrated a significant increase in hepcidin synthesis during infection and inflammation, driven by stimulation from interleukin-6 (IL-6). Consequently, hepcidin is categorized as an acute-phase protein and a component of the innate immune system.[8,10,11] In the context of acute appendicitis, which often develops from mechanical obstruction of the appendiceal lumen or inflammation in adjacent appendiceal tissues, there is typically an increase in acute-phase proteins. Therefore, we hypothesize that hepcidin, one of these acute-phase proteins, will also show elevated levels in the pathology of acute appendicitis.

In this study, we measured the blood hepcidin levels in patients who underwent surgery based on a preliminary diagnosis of AA. Our goal was to determine the diagnostic value of hepcidin in adult AA patients.

MATERIALS AND METHODS

This multicenter prospective study was conducted in two tertiary emergency departments from April 2018 to May 2019, following preliminary approval by the Ethics Committee (decision number 2018/109). The average annual admission to the emergency services of the study centers is approximately 100,000. We included patients who presented to the emergency department with abdominal pain, were diagnosed with AA based on clinical findings, abdominal USG, and CT, and underwent surgical treatment. The exclusion criteria were patients receiving iron supplements, blood transfusions, those with hemolysis, anemia, iron deficiency, hemochromatosis, erythropoiesis, hematological cancer diseases, pregnancy, trauma patients, acute cerebrovascular disease, heart failure, liver disease (including liver cirrhosis, liver failure, hepatitis, hepatocellular carcinoma, non-alcoholic fatty liver disease), lung disease, hypoxia, inflammatory bowel disease, or those with a focus of infection other than AA identified in the post-operative pathology report.[12,13] Patients with incomplete data in the data collection form or the hospital information management system were also excluded. Healthy volunteers over the age of 18 who consented to participate were included as the control group. Demographic characteristics, symptoms, physical examination findings, laboratory parameters, Alvarado scores, imaging results (abdominal USG and abdominal CT), and post-operative pathology results were recorded on the data collection form. Serum hepcidin levels were biochemically measured in the study and control groups. A definitive diagnosis of AA was confirmed via post-operative pathology reports. This study comprised three groups: patients whose post-operative pathology report confirmed AA (Group A), those with diagnoses other than AA (Group B), and the control group.

Analysis of Serum Hepcidin Levels

Venous blood samples were collected from patients upon admission using serum separator tubes, which were filled to the capacity allowed by the vacuum. After centrifugation, the plasma was separated and stored at -80 °C. At the conclusion of the study's case collection period, hepcidin levels were measured in the blood serum of all groups using the Cloud Clone (USCNK) brand (Wuhan, China) enzyme-linked immunosorbent assay (ELISA) kit. The measurements, expressed in pg/mL, followed the manufacturer's recommendations (detection range: 32-20,000 pg/mL).

WBC and CRP values were also measured in the blood samples taken at the time of admission.

Statistical Analysis

All statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences) v28 (IBM Inc., Chicago, IL, USA). Power analysis revealed that with α=0.05 and a power of 1-β=0.91, and a moderate difference (Cohen's effect size=0.3), at least 50 participants per group were needed to detect differences among the AA, non-AA, and control groups. Descriptive statistics, categorical variables, and numerical variables were assessed using the Kolmogorov-Smirnov test to determine conformity to normal distribution. For parameters fitting normal distribution, t-tests and for those not fitting, Mann-Whitney U tests were used in the comparison of paired groups. Analysis of Variance (ANOVA) and Kruskal-Wallis tests were employed for intergroup comparisons for parameters fitting and not fitting normal distribution, respectively. If the ANOVA results were significant with homogeneity across groups in pairwise comparisons, the Tukey test was applied. In cases of significant ANOVA results without group homogeneity, Tamhane's test was used.[14,15] For significant Kruskal-Wallis tests, pairwise comparisons were conducted using the Mann-Whitney U test with Bonferroni correction. Correlation coefficients and statistical significance were calculated using Pearson's test for variables that conformed to a normal distribution and Spearman's test for variables that did not. For variables with significant cut-off values, Receiver Operating Characteristics (ROC) curve analysis was conducted along with sensitivity and specificity assessments. To predict AA, significant levels

Table 1. Demographic characteristics of the groups

Characteristics	Group A[a] n=94	Group B[b] n=16	Control[c] n=42	p Value
Sex				
Male	61 (71.4%)	8 (50.0%)	26 (61.9%)	$p^{a,b,c}>0.05$
Female	33 (28.6%)	8 (50.0%)	16 (38.1%)	$p^{a,b,c}>0.05$
Age, mean±SD (min-max)	39.6 (18.1) (18-93)	34.2 (14.0) (18-59)	25.0 (8.7) (18-53)	$p^{a,b}=0.340$ $p^{a,c}<0.001$ $p^{b,c}<0.001$
Time to Onset of Symptoms (hours), mean (SD) (min-max)	14.4 (14.1) (2-72)	11.1 (11.5) (2-48)	–	
Alvarado Score, mean (SD) (min-max)	5.0 (1.4) (3-10)	6.8 (1.6) (3-8)	–	
Right Lower Quadrant Tenderness				
Yes	91 (96.8%)	16 (100.0%)	–	
No	3 (3.2%)	0 (0.0%)	–	
Leukocytosis				
Yes	75 (79.8%)	7 (43.7%)	No leukocytosis	
No	19 (20.2%)	9 (56.3%)		
Pain Migration				
Yes	53 (56.4%)	6 (37.5%)	–	
No	41 (43.6%)	10 (62.5%)	–	
Lack of Appetite				
Yes	47 (50.0%)	5 (31.3%)	–	
No	47 (50.0%)	11 (68.7%)	–	
Nausea and Vomiting				
Yes	53 (56.4%)	8 (50.0%)	–	
No	41 (43.6%)	8 (50.0%)	–	
Rebound				
Yes	60 (63.8%)	6 (37.5%)	–	
No	34 (36.2%)	10 (62.5%)	–	
Body Temperature >37.3 °C				
Yes	19 (20.2%)	2 (12.5%)	–	
No	75 (79.8%)	14 (87.5%)	–	
Left Shift in Neutrophils				
Yes	75 (79.8%)	7 (43.7%)	–	
No	19 (20.2%)	9 (56.3%)	–	
USG Imaging				
Positive	7 (7.4%)	1 (12.5%)	–	
Negative	19 (20.2%)	2 (6.3%)	–	
Not Performed	68 (72.3%)	13 (81.2%)	–	
CT Imaging				
Positive	80 (85.1%)	4 (25.0%)	–	
Negative	0 (0.0%)	10 (62.5%)	–	
Not Performed	14 (14.9%)	2 (12.5%)	–	

min: Minimum; max: Maximum; USG: Ultrasonography; CT: Computed tomography.

of WBC count, CRP, and hepcidin were analyzed using multivariate logistic regression. Statistical significance was set at p values <0.05.

RESULTS

The study included 125 patients diagnosed and operated on for AA in the emergency department, alongside 42 healthy volunteers as the control group. Fifteen patients were excluded due to incomplete study forms, and serum hepcidin levels were not measured in these cases. The postoperative histopathology results of the patients were analyzed. Histopathological examination was conducted on 110 patients who underwent surgery with a diagnosis of AA. Of these, the pathology reports of 94 patients were classified as Group A, while the reports of 16 patients were categorized into Group B. Histopathologic evaluation revealed that Group B comprised 8 patients with normal appendix vermiformis and 8 with mesenteric lymphadenitis. Right lower quadrant pain was the most common symptom prompting emergency department visits among the study participants. Sociodemographic characteristics are detailed in Table 1. CT was the preferred diagnostic imaging modality, used by 85.1% of Group A and 87.5% of Group B patients. Of the Group B patients, 62.5% underwent surgery despite CT imaging results not indicating AA (Table 1).

A statistically significant difference in median serum hepcidin levels was observed between the groups. The comparison of serum levels across groups is shown in Table 2.

When analyzing the relationship between hepcidin, WBC, and CRP, significant positive correlations were found: a strong correlation between hepcidin and WBC (r=0.603), a moderate correlation between hepcidin and CRP (r=0.532), and between WBC and CRP (r=0.460), all with p<0.001. The area under the curve (AUC) for ROC analysis, which measured the diagnostic value of serum hepcidin, was 0.76 (p<0.001, 95% confidence interval [CI] 0.80-0.97) (Fig. 1). As serum hepcidin values increased, the specificity of hepcidin for diagnosing appendicitis also increased. In our study, the serum hepcidin cut-off value for diagnosing AA was set at >1320.51; based on this value, its sensitivity was 95.74%, specificity 62.5%, positive predictive value (PPV) 93.7%, and negative predictive value (NPV) 75.0%. The WBC cut-off was set at >11000, with a sensitivity of 79.79%, specificity of 93.7%, PPV of 98.7%, and NPV of 44.1%. The CRP cut-off was established at >2.2, with a sensitivity of 46.81%, specificity of 87.5%, PPV of 95.7%, and NPV of 21.9%. The NPV of serum hepcidin was found to be superior to that of WBC and CRP (Table 3).

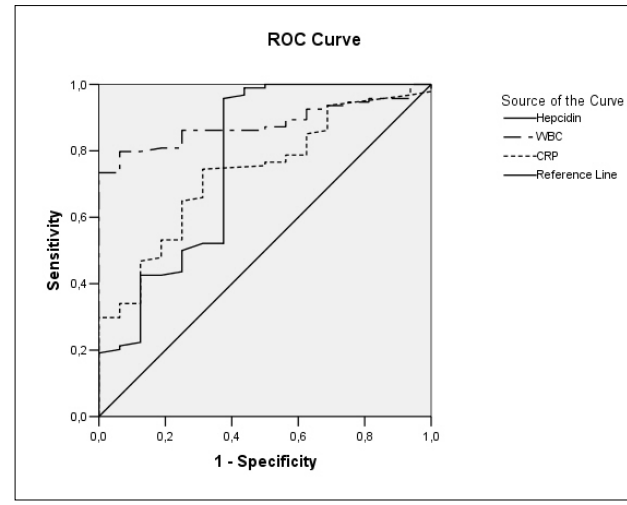

Figure 1. Receiver operating characteristic (ROC) analysis chart performed to measure the diagnostic value of white blood cell (WBC) count, C-reactive protein (CRP), and hepcidin in patients with acute appendicitis.

Table 2. Comparison of blood levels of white blood cell (WBC), C-reactive protein (CRP), and hepcidin among patient groups

	Group A[a] n=94 (mean±SD)	Group B[b] n=16 (mean±SD)	Control Group[c] n=42 (mean±SD)	p value
WBC (cells/mm^3)	14051±3832	9479±1405	7443±1843	<0.001α
				$p^{a,b}$<0.001γ, $p^{a,c}$<0.001γ, $p^{b,c}$<0.001γ
CRP (mg/L)				
	3.77±4.4	0.96±1.2	0.21±0.2	<0.001β
				$p^{a,b}$=0.003δ, $p^{a,c}$<0.001δ, $p^{b,c}$<0.012δ
Hepcidin (pg/mL)				
	1750±285	1349±381	1066±225	<0.001α
				$p^{a,b}$=0.002γ, $p^{a,c}$<0.001γ, $p^{b,c}$=0.034γ

α: Results based on ANOVA (Analysis of Variance) test; β: Results based on Kruskal-Wallis test; γ: Results based on Post Hoc Tamhane's test; δ: Results based on Bonferroni corrected Mann-Whitney U-test; WBC: White blood cell count; CRP: C-Reactive protein.

Table 3. Sensitivity and specificity of hepcidin in diagnosing acute appendicitis

Hepcidin (pg/mL)	Sensitivity (95% CI)	Specificity (95% CI)	+LR	-LR	PPV (%)	NPV (%)
>1320	95.7% (89.5-98.8)	62.5% (35.4-84.8)	2.5	0.06	93.7	75.0
>1679	50.0% (39.5-60.5)	75.0% (47.6–92.7)	2.0	0.6	92.2	51.4
>1929	21.2% (13.5-30.9)	93.7% (69.8-99.8)	3.4	0.8	93.0	20.6

+LR: Positive likelihood ratio; -LR: Negative likelihood ratio; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

DISCUSSION

Hepcidin, an acute-phase protein, binds to ferroprotein, disrupting endolysosomes. Elevated hepcidin levels reduce plasma iron concentrations, diminishing iron availability for bacterial use and thereby inhibiting bacterial proliferation.[16] Hepcidin production is regulated by inflammation, body iron levels, tissue damage, and oxygenation status. During inflammation, hepatocytes increase hepcidin production via the activation of the interleukin-6 (IL-6) and signal transducer and activator of transcription 3 (STAT3) pathways.[17] In an experimental study, mice analyzed 3, 6, and 10 hours post-infection with V. vulnificus demonstrated a sharp increase in hepatic hepcidin mRNA and serum hepcidin levels at 6 hours post-infection. It was found that hepcidin levels stabilized at high levels 10 hours after infection.[18] Beltran et al. reported that CRP levels increased gradually at 12, 24, and 48 hours from symptom onset to diagnosis and began to decrease after reaching the highest value within 12 hours of the diagnosis period.[19]

In the study conducted by Asan et al., the median serum hepcidin levels in healthy volunteers, with a mean age of 35.23±11.76, were determined to be 890.0 (495.0-1,716.9) pg/mL.[20] In patients with Ulcerative Colitis and Crohn's Disease, mean serum hepcidin levels were 4090±1005 pg/mL and 3798±1337 pg/mL, respectively.[21] Increased hepcidin levels have been observed in other inflammatory conditions such as infections, systemic inflammatory diseases, inflammatory bowel disease, neonatal sepsis, and rheumatoid arthritis.[22-25] Moro et al. reported that patients with bloodstream infections exhibited increased hepcidin levels during the acute phase, which decreased during the recovery phase once the infection was controlled.[17]

Kaiser et al. found a significant increase in serum hepcidin levels in pediatric appendicitis patients compared to the healthy control group, and patients with complicated AA had higher serum hepcidin levels than those with non-complicated AA.[8] Ilhan et al. examined serum hepcidin levels in 40 AA patients and found that average hepcidin levels during the acute inflammation period were 658.88±609.31 ng/mL. They also observed that hepcidin levels decreased during the recovery period.[26] In our study, we expanded the patient sample and compared serum hepcidin levels in patients not diagnosed with acute appendicitis postoperatively. It was also found that hepcidin levels in patients with positive histopathology for AA post-surgery increased more than those in patients with negative histopathology. In our study, the AUC for serum hepcidin in AA patients was 0.76 in the ROC analysis. Accordingly, we suggest that the level of hepcidin increases in appendiceal inflammation due to its role in the inflammatory response. Literature shows many biomarkers are associated with AA with WBC and CRP being the most widely used. According to various studies, the sensitivity of WBC in diagnosing AA ranges from 67% to 97.8%, specificity from 31.9% to 90.8%, NPV from 77.9% to 82%, and PPV from 42% to 91.8%.[27,28] In the study conducted by Demircan et al., when the WBC cut-off value was set at >10000 for diagnosing AA, the sensitivity was 98.77%, specificity 75.0%, PPV 98.8% and NPV 75.0%.[29] In a meta-analysis and systematic review by Yu et al., evaluating the accuracy of CRP in diagnosing AA, the sensitivity was found to be 39-73%, specificity 58-97%, positive likelihood ratio (+LR) 4.48, and negative likelihood ratio (-LR) 0.49. (30) The results of our study align similarly with the literature.[30] In our correlation analysis, hepcidin showed a strong positive correlation with WBC and a moderate positive correlation with CRP. We believe that the diagnostic value of hepcidin for AA could be enhanced when used in conjunction with other inflammatory markers.

If AA is overlooked in the emergency room, it can progress to life-threatening complications such as perforation, intra-abdominal abscess, and sepsis. Despite advances in medical diagnostics, AA is one of the most frequently missed surgical diagnoses. In addition to clinical findings, scoring systems are also employed in the diagnosis of surgical pathologies. Among these, the Alvarado scoring system is most commonly used by emergency physicians.[27,31] This system consists of eight parameters: three based on symptoms, three on physical examination findings, and two on laboratory measurements. A score of 4 or below suggests appendicitis is unlikely, whereas a score of 7 or above indicates surgery is recommended. However, prospective studies have indicated that the Alvarado scoring system alone is not sufficient for diagnosing AA.[31,32] According to our records, the mean Alvarado score of patients in Group A was higher than that of Group B, and a significant difference was observed in the comparison of serum hepcidin levels between these groups. Consequently, we

believe that patients with high Alvarado scores and elevated serum hepcidin levels may be more likely to have AA. Due to reduced patient contact during the Coronavirus Disease 2019 (COVID-19) pandemic and an increase in malpractice cases, physicians often resort to CT scans, which are more sensitive for diagnosing surgical pathologies such as AA. Although many clinicians request an USG for diagnosing AA due to its advantages of no radiation exposure and lower cost, they frequently proceed to CT scans due to the dependency on radiologist's expertise. In our study, the histopathological results of four patients diagnosed with AA via CT did not confirm AA. Since patients presenting with abdominal pain often have atypical presentations, we advocate for correlating all available findings rather than relying solely on imaging methods to diagnose AA.

Limitations

While AA is an acute-onset disease, the time lag between the onset of appendicitis inflammation and its detection in the emergency room may influence the measurement of peak hepcidin levels in the blood. The uneven distribution of cases across groups and the presence of other non-excluded inflammations that may affect hepcidin levels are limitations of this study. Although we excluded patients with comorbidities that could influence serum hepcidin levels, the younger average age of the control group compared to the patient group also represents a limitation.

CONCLUSION

This study is one of the most comprehensive to demonstrate that the serum hepcidin biomarker is valuable in the diagnosis of acute appendicitis. We found that serum hepcidin levels were significantly higher in adult patients with surgically confirmed AA compared to both the control group and patients with surgically confirmed non-AA pathology. This finding suggests that serum hepcidin may be valuable in preventing unnecessary appendectomies. When comparing the sensitivity and specificity rates of hepcidin with those of other inflammatory markers reported in previous studies, hepcidin shows similar efficacy. These results indicate that hepcidin is involved in the inflammatory process of acute appendicitis. We believe that serum hepcidin levels are a laboratory marker that should be evaluated alongside other findings in diagnosing AA in adult patients. However, future research is necessary to establish the normal reference values of hepcidin in healthy adults, which would enable its use as a potential biomarker for excluding appendicitis in the emergency department.

Ethics Committee Approval: This study was approved by the Ordu University, Faculty of Medicine Ethics Committee (Date: 10.05.2018, Decision No: 2018-109).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Akut apandisitte serum hepcidinin tanısal değeri

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AMAÇ: Akut apandisit (AA), acil servise karın ağrısı şikayetiyle başvuran hastalarda akut karın nedenleri arasında birinci sırada yer almaktadır. Literatürde serum hepsidin ile AA arasındaki ilişkiyi inceleyen sınırlı sayıda çalışma bulunmaktadır. Çalışmanın amacı AA ön tanısıyla ameliyat edilen hastalarda serum hepcidin düzeylerini ölçmek ve bu parametrelerin AA tanısında biyokimyasal belirteç olarak kullanılıp kullanılamayacağını araştırmaktır.
GEREÇ VE YÖNTEM: Nisan 2018 ile Mayıs 2019 tarihleri arasında acil servise başvuran, AA tanısıyla ameliyat edilen 18 yaş ve üzeri hastalar çalışmaya alındı. Çalışmaya cerrahi sonrası patoloji sonucu AA ile uyumlu olan 94 hasta (Grup A), cerrahi sonrası patoloji sonucu AA ile uyumlu olmayan 16 hasta (Grup B) ve 42 sağlıklı kontrol grubu dahil edildi. Venöz kan örneklerinden serum hepsidin düzeyleri ölçüldü.
BULGULAR: Grup A hastaların ortalama hepsidin düzeyleri 1750±285 pg/mL, Grup B hastalarınınki 1349±381 pg/mL ve kontrol grubununki 1066±225 pg/mL olarak belirlendi. Serum hepsidin düzeylerinin karşılaştırılmasında Grup A ve kontrol grubunu arasında istatistiksel olarak anlamlı farklılık gösterdiği görüldü ($p<0.05$).
SONUÇ: Hepsidin AA hastalarında kontrol grubuna ve cerrahi olarak AA dışı patoloji saptanan hastalara göre anlamlı olarak yüksek bulundu. Hepsidin akut apandisit tanısına yardımcı olarak kullanılabilir.

Anahtar sözcükler: Akut apandisit; erişkin; hepsidin; inflamasyon; karın ağrısı.

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