ORIGINAL ARTICLE

Evaluation of factors predicting appendiceal tumoral lesions in patients undergoing appendectomy for acute appendicitis

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ABSTRACT

BACKGROUND: Tumoral lesions are a relatively rare cause of acute appendicitis. Accurate pre-operative diagnosis is essential to provide appropriate treatment. The aim of this study was to evaluate factors that may increase diagnostic rate of appendiceal tumoral lesions in patients undergoing appendectomy.

METHODS: A retrospective review of a large cohort of patients who underwent appendectomy for acute appendicitis from 2011 to 2020 was undertaken. Demographics, clinicopathologic findings, and pre-operative laboratory values were recorded. Univariate and multivariate logistic regression and receiver-operating characteristic curve analysis were performed to identify the factors that predict appendiceal tumoral lesions.

RESULTS: A total of 1400 patients were included in the study, with median age of 32 (range, 18–88) years, and of whom 54.4% were male. Overall, 2.9% (n=40) of patients had appendiceal tumoral lesions. Multivariate analysis revealed that age (Odds Radio [OR] 1.06, 95% confidence interval [CI] 1.03–1.08) and WBC count (OR 0.84, 95% CI 0.76–0.93) were independent predictors of appendiceal tumoral lesions. The optimal cutoff age was 37 years old (AUC: 0.79; sensitivity: 82.0%; specificity: 62.0%). WBC count <10×10^9/L was another independent predictive factor (AUC: 0.69, sensitivity: 74%; specificity: 60%).

CONCLUSION: Predicting an appendiceal tumoral lesion preoperatively is critical to ensure a favorable post-operative outcome. Higher age and low WBC counts appear to be independent risk factors for an appendiceal tumoral lesion. In case of doubt and in the presence of these factors, wider resection should be favored over appendectomy only to provide a clear surgical margin.

Keywords: Acute appendicitis; appendiceal tumor; malignant; neoplasm.

INTRODUCTION

Acute appendicitis is a frequent surgical emergency worldwide. The cause is always a luminal obstruction which is usually due to fecal stasis, fecaliths, or lymphoid hyperplasia. Besides, there are unusual causes of obstruction such as neoplasms, organic or inorganic foreign materials, barium contrast, and parasites.[1] Regardless of cause, most of the cases are treated surgically and an appendectomy remains the gold standard of care.[2,3] Although the diagnosis is mostly acute appendicitis, the underlying pathogenesis of appendicitis cannot be determined without an appropriate histopathological examination. However, in some cases, unexpected benign or malignant lesions may be encountered in the specimens including simple mucocele, epithelial neoplasms, or neuroendocrine tumor (NET) of appendix.[4,5]

Appendiceal lesions are rare and usually discovered incidentally during imaging studies, endoscopy, surgery, or during pathological evaluation of the specimen.[6,7] Although most of the appendiceal lesions are excised without complication during appendectomy, in some cases, resection margin positivity

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or iatrogenic perforation due to careless dissection causes dissemination of the disease in the peritoneal cavity, especially in patients with premalignant or malignant lesions.[8]

Some findings detected in pre-operative imaging studies can help determine mucocele, advanced appendiceal malignancy, or peritoneal disease, but imaging often cannot differentiate benign pathologies from malignant lesions.[9] Therefore, a thorough understanding of the factors that distinguish appendiceal tumoral lesions from other benign appendiceal lesions is necessary to optimize the evaluation, and appropriate surgical management. The aim of this study was to evaluate clinicopathological and pre-operative characteristics that predict appendiceal tumoral lesions in patients undergoing appendectomy for acute appendicitis.

MATERIALS AND METHODS

Study Design

Data of all adult patients who underwent an appendectomy for acute appendicitis at Ankara University from January 2011 to December 2020 were retrospectively reviewed. Patients who underwent incidental appendectomy as a part of an elective operation were excluded. The Ankara University School of Medicine Ethics Committee approved this study (Approval Date and No: 01.08.2022, i07-407-22).

Data Collection

Data about age, gender, ASA score, pre-operative laboratory data, imaging investigations, surgical procedures, length of hospital stay, and 30-day outcomes were obtained. Histopathological examination confirmed the diagnosis of appendicitis. Patients with gangrenous appendicitis, appendicular abscess, and/or perforation detected through imaging studies, operative exploration, or pathology assessments were defined as complicated appendicitis. Negative appendectomy was defined as microscopically normal appendix on histopathological examination without evidence of inflammation, fibrosis, and neoplasm.

Outcomes

The primary outcome was the incidence of appendiceal tumoral lesions in adult patients undergoing appendectomy for acute appendicitis. Appendiceal tumoral lesions were defined according to the World Health Organization (WHO) classification of digestive tumors.[5] Although mucocele is not classified as a tumoral lesion by the WHO, patients with pathologically confirmed mucocele were also included in the study. Since it is not possible to differentiate a simple mucocele and a neoplastic lesion with imaging studies preoperatively.

Statistical Analysis

Normality was assessed using the Shapiro–Wilk test. Normally distributed data were presented as mean and standard deviation, non-normally distributed data as median with minimum to maximum ranges, and categorical data as frequencies (n) and percentages (%). Student's t tests and Wilcoxon Mann–Whitney U tests were used to compare continuous variables. Pearson χ^2 and Fisher's exact tests were used to compare categorical variables. Factors found to be significant ($p<0.20$) on univariate analysis were included in the multivariate logistic regression model to determine the independent effect of these variables on the risk of appendiceal tumoral lesions. If variables were found to be collinear, then the potentially more relevant parameter was selected for the multivariable model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic values for each outcome based on maximum Youden index. All statistical tests were two-sided and the significance level was set at $p<0.05$. All statistical analyses were performed in Statistical Package for the Social Sciences, version 16.0 (IBM®, Chicago, USA). A forest plot was constructed to illustrate findings of the multivariate analysis, using GraphPad Prism version 8.0.1 for Windows (GraphPad Software Inc., CA, USA).

RESULTS

A total of 1400 patients were included in the study, with median age of 32 (range, 18–88) years, and of whom 54.4% were male. While, 847 (60.5%) cases were completed laparoscopically, 553 (39.5%) appendectomies were performed

Table 1. Demographic characteristics, clinicopathological features, and postoperative outcomes of the patients with acute appendicitis (n=1400)

Characteristics	
Age (years)*	32 (range, 18–88)
Male gender, n (%)	761 (54.4)
ASA score, n (%)	
1–2	1380 (98.6)
3–4	20 (1.4)
Appendix diameter (mm)*	9 (range, 2.3–25)
WBC (×10⁹/L)*	12.6 (range, 0.1–28.7)
Neutrophil (×10⁹/L)*	9.7 (range, 0.05–25.8)
C-reactive protein (mg/L)*	20.7 (range, 0.1–498)
Surgical technique, n (%)	
Open	847 (60.5)
Laparoscopic	553 (39.5)
Complicated appendicitis, n (%)	165 (11.8)
Negative appendectomy, n (%)	91 (6.5)
Appendiceal tumoral lesions, n (%)	40 (2.9)

ASA: American Society of Anesthesiologists; CT: Computed tomography; USG: Ultrasonography; WBC: White blood cell. *The values are given as the median, with the range in parentheses.

open. The negative appendectomy rate was 6.5% (n=91). The demographic characteristics, clinicopathological features, and post-operative outcomes of the patients are presented in Table 1.

Overall, 2.9% (n=40) of patients had appendiceal tumoral lesions. The pathological results included sessile serrated lesion (SSL) in 11 patients, low-grade mucinous neoplasm in 10 patients, hyperplastic polyp in nine patients, mucocele in three patients, adenocarcinoma in two patients, and tubular adenoma in one patient (Table 2). Out of other 1360 patients, the diagnosis was lymphoid hyperplasia for 126 (9.3%), granulomatous appendicitis for 6 (0.4%), and appendiceal diverticulitis for 2 (0.2%).

The comparative analysis of patients with appendiceal tumoral lesions and those with other appendiceal pathologies is summarized in Table 3. There was no difference between the two groups with respect to gender (p=0.127), lymphocyte (p=0.899), C-reactive protein (p=0.851), length of hospital stay (p=0.066), or 30-day complication (p=0.325). Patients with appendiceal tumoral lesions were significantly older (55 years vs. 29 years, p<0.001), had a significantly higher rate of ASA score 3 or 4 (17.5% vs. 1.0%, p<0.001), and had a significantly greater diameter of the appendix (10 mm vs. 9 mm, p=0.022) than those without tumoral lesions. Pre-operative neutrophil and white blood cell (WBC) counts were also significantly lower in patients with appendiceal tumoral lesions (p<0.001 and p<0.001, respectively).

Logistic regression was performed to determine the factors that predicted appendiceal tumoral lesions. Univariate analysis showed that age, female gender, ASA score 3–4, appendix diameter, WBC count, and neutrophil count were associated with an increased risk of tumoral lesions. Because age and ASA score as well as WBC and neutrophil counts were found to be collinear, only age and WBC were entered into the multivariate model. Multivariate regression analysis revealed that age (OR 1.06, 95% CI 1.03–1.08) and WBC count (OR 0.84, 95% CI 0.76–0.93) were independent predictors of appendiceal tumoral lesions (Fig. 1).

ROC curve analysis was performed to determine the optimal cutoff values for age and WBC count. Patient age with a cutoff value of 37 years generated an AUC of 0.79 (95% CI 0.73–0.85) with a sensitivity of 82.0% and a specificity of 62.0% for appendiceal tumoral lesions versus control (p<0.001). WBC count of patients with tumoral lesions versus the control

Table 2. Pathological findings of 40 patients with appendiceal tumoral lesions

Pathological findings	n (%)
Sessile serrated lesion (SSL)	11 (27.5)
Low-grade mucinous neoplasm	10 (25.0)
Hyperplastic polyp	9 (22.5)
Mucocele	4 (10.0)
Neuroendocrine tumor	3 (7.5)
Mucinous adenocarcinoma	2 (5.0)
Tubular adenoma	1 (2.5)

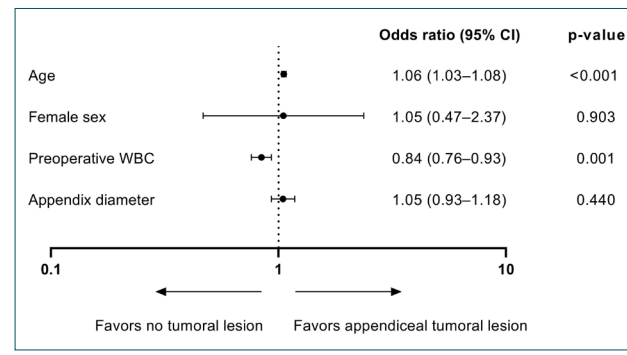

Figure 1. Forest plot of significant factors in the multivariate analysis for diagnosis of appendiceal tumoral lesions in patients undergoing appendectomy.

Table 3. Comparison of the patients with isolated appendiceal tumoral lesions and those with other appendiceal pathologies

	Appendiceal tumoral lesions (n=40)	Other appendiceal pathologies (n=1360)	p-value
Age (years)*	55 (range, 23–83)	29 (range, 18–88)	<0.001
Male gender, n (%)	17 (42.5)	744 (54.7)	0.127
ASA score 3–4, n (%)	7 (17.5)	13 (1.0)	<0.001
Appendix diameter (mm)*	10 (range, 7–16)	9 (range, 2.3–25)	0.022
WBC ($\times 10^9$/L)*	9.3 (range, 3.9–15.9)	12.8 (range, 0.1–28.7)	<0.001
Neutrophil ($\times 10^9$/L)*	7.0 (range, 2.0–14.2)	9.8 (range, 0.05–25.8)	<0.001
C-reactive protein (mg/L)*	21.3 (range, 0.7–338)	20.7 (range, 0.1–498)	0.851
Laparoscopic appendectomy, n (%)	20 (50.0)	533 (39.2)	0.168
Complicated appendicitis, n (%)	10 (25.0)	155 (11.4)	0.020

ASA: American Society of Anesthesiologists; WBC: White blood cell. *The values are given as the median, with the range in parentheses.

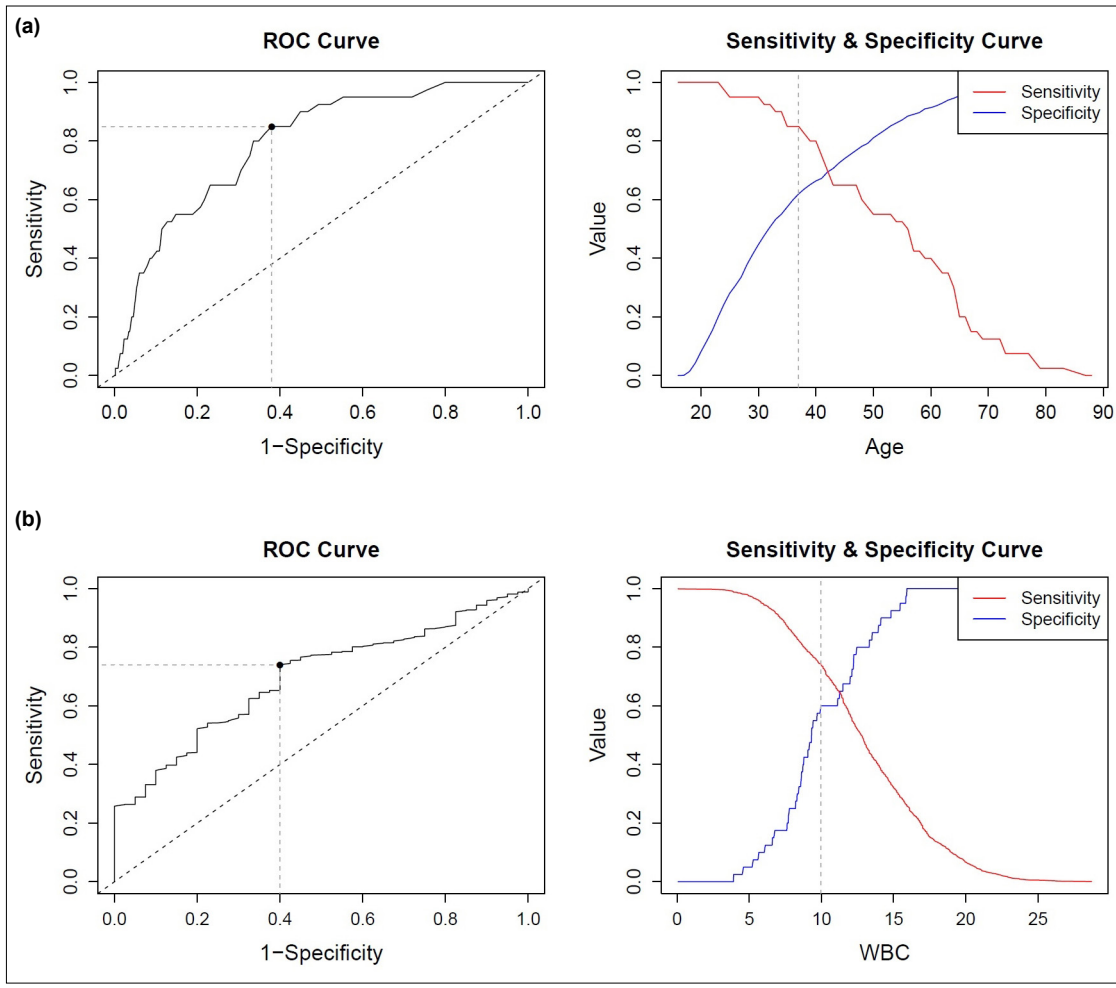

Figure 2. ROC analysis of factors independently predicting appendiceal tumoral lesions.

with a cutoff value of 10×10⁹/L μg/mL generated an AUC of 0.69 (95% CI 0.62–0.76, p<0.001) with a sensitivity of 74.0% and a specificity of 60.0% (Fig. 2).

DISCUSSION

Although appendicular neoplastic lesions are rare, they can be annoying since they may require a secondary operation, and these additional surgical interventions may adversely affect patient prognosis. Especially for premalignant or malignant lesions, removal with a clear surgical margin and avoiding perforation are important factors affecting the postoperative outcome of the patients.[10] Therefore, the incidence of appendiceal tumoral lesions and the factors predicting them gain importance. In this study, we aimed to identify the clinicopathological factors that predict appendiceal tumoral lesions in patients undergoing appendectomy for acute appendicitis.

The incidence of appendiceal tumoral lesion was found to be 2.9% in this study of 1400 individuals with a mean age of 32 years, which was similar to the findings of prior studies that indicated rates ranging from 0.9% to 3.7%.[11,12] This study also demonstrated that 90% of appendiceal tumoral lesions were mucinous lesions, while only 7.5% were NET. SSLs, low-grade mucinous neoplasm, and hyperplastic polyp were the most common pathological findings. Older studies reported that the most common appendiceal tumors were NET and they were approximately 50% of all appendiceal tumoral lesions.[11,12] Recent studies, on the other hand, have reported the NET rate as between 11% and 20%.[6,13,14] The inconsistency between older and newer studies is thought to be due to the publication of consensuses on nomenclature of appendiceal tumoral lesions and possibly a more dense sampling of specimens in pathology.[4,5,15] Kepil has reported that multiple and dense sampling of appendix specimens increase the incidence of detection of unusual lesions.[15]

The risk of appendiceal tumor increases with age and the mean age at diagnosis varied among the appendiceal tumor types. The mean age at diagnosis for NET is over 40; for mucinous lesions, it is about 60 years of age.[13,16–18] However, to the best of our knowledge, there is no age cutoff analysis for appendiceal tumoral lesions. In this study, age was found to be a significant risk factor of occurrence of tumoral lesions. The optimal cutoff was 37 with a sensitivity of 82.0%

and a specificity of 62.0%. WBC count <10×10^9/L was another independent predictive factor for appendiceal tumoral lesions. In patients with these two predictive factors, appendectomy should be performed with a clear surgical margin, and if necessary, it may be recommended to include partial cecum during appendectomy while preserving ileocecal valve. Ensuring a clear surgical margin provides curative results in all appendiceal premalignant lesions and NETs <2 cm.[19,20] Even for T1 mucinous adenocarcinomas, it was stated that if the appendectomy specimen has a clear surgical margin, the patient could be followed up without right hemicolectomy.[21] It should also be recognized that some authors recommend appendectomy with excision of mesoappendix, if only appendectomy is preferred in a patient with suspicious appendiceal morphology.[22] Excision of mesoappendix provides to analyze the regional lymph nodes.

Although not significant in the multivariate analysis, an increase in appendix diameter was found to be associated with tumoral lesion in the univariate study. However, this is controversial. Because the typical dimension of the appendix is a contentious issue. The upper limit of the normal appendix diameter is considered to be 6 mm, and this value is determined by ultrasound measurements in several studies.[23] On the other hand, a study that examined normal appendix diameters using computed tomography in patients who did not have acute appendicitis found that the maximum diameter might reach 12.8 mm.[23] However, according to a recent study, an isolated distally localized appendiceal dilatation with a proximal segment of morphologically normal appendix is strongly correlated with an underlying malignant lesion. If the dilatation exhibits mural calcification is larger than 2 cm in diameter, and there is no periappendiceal stranding, a neoplastic lesion is strongly suspected.[24]

Limitations of this study include the retrospective design and limited generalizability, given that this study was carried out in a single center. Nevertheless, the large patient cohort strengthens the validity of our findings. However, to the best of our knowledge, this is the first report in the literature investigating predictive factors for appendiceal tumoral lesions.

Conclusion

Although appendiceal tumoral lesions are uncommon, a surgeon's lifetime possibility of encountering an appendiceal tumoral lesion is higher than expected due to the high number of appendectomies performed. Predicting an appendiceal tumoral lesion preoperatively is critical to avoiding a postoperative catastrophic event such as peritoneal dissemination due to tumor perforation or resection margin positivity. Age and low WBC counts appear to be independent risk factors for an appendiceal tumoral lesion. Wider resection should be favored over a simple appendectomy in the presence of these factors, especially if the proximal appendix does not appear morphologically normal.

Ethics Committee Approval: This study was approved by the Ankara University Human Research Ethics Committee (Date: 01.08.2022, Decision No: i07-407-22).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Akut apandisit nedeniyle apendektomi yapılan hastalarda apendiks tümöral lezyonlarını öngören faktörlerin değerlendirilmesi

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AMAÇ: Tümöral lezyonlar akut apandisitin nadir nedenleri arasında yer alır. Böyle bir durumda uygun tedaviyi sağlamak için ameliyat öncesi doğru tanı önemlidir. Bu çalışmanın amacı, apendektomi yapılan hastalarda apendiks tümöral lezyonlarının tanı oranını artırabilecek faktörleri değerlendirmektir.
GEREÇ VE YÖNTEM: Akut apandisit nedeniyle 2011–2020 arası apendektomi yapılan geniş hasta grubu geriye dönük olarak incelendi. Hastaların demografik özellikleri, klinikopatolojik bulguları ve ameliyat öncesi laboratuvar değerleri kaydedildi. Apendiks tümöral lezyonlarını tahmin eden faktörleri belirlemek için tek değişkenli ve çok değişkenli lojistik regresyon ve ROC analizi yapıldı.
BULGULAR: Çalışmaya ortanca yaşı 32 (18–88) olan ve %54.4'ü erkek olan toplam 1400 hasta dahil edildi. Genel olarak, hastaların %2.9'unda (n=40) apendiks tümöral lezyonu tespit edildi. Çok değişkenli analiz, yaş (OR 1.06, %95 GA 1.03–1.08) ve lökosit sayısının (OR 0.84, %95 GA 0.76–0.93) apendiks tümöral lezyonları için bağımsız belirteçler olduğunu ortaya koydu. Yaşın >37 (EAA: 0,79; duyarlılık: %82.0; özgüllük: %62.0) ve lökosit sayısının $<10\times10^9$/L olması (EAA: 0.69; duyarlılık: %74; özgüllük: %60) tümöral lezyon bulunma ihtimali için eşik değerler olarak tespit edildi.
TARTIŞMA: Apendiks tümöral lezyonunu ameliyat öncesi olarak tahmin etmek, olumlu bir ameliyat sonrası sonuç elde edebilmek için kritik öneme sahiptir. Yaşlı hasta ve düşük lökosit sayıları apendiks tümöral lezyonları için bağımsız risk faktörleri olarak tespit edilmiştir. Şüphe durumunda ve bu faktörlerin varlığında sadece apendektomi yapmak yerine temiz cerrahi sınırı sağlayacak şekilde geniş rezeksiyon sadece apendektomiye tercih edilebilir.
Anahtar sözcükler: Akut apandisit; apendisyal tümör; malign; neoplazm.

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