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Predicting appendiceal tumors among patients with appendicitis

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Abstract

Background—As non-operative management of appendicitis gains popularity, vigilance for appendiceal tumors becomes increasingly important. We hypothesized that among patients presenting with acute appendicitis, those with advanced age, multiple comorbidities, atypical presentation, and complicated appendicitis would be more likely to have underlying appendiceal tumors.

Methods—We performed a 4-year retrospective cohort analysis of 677 consecutive adult patients who underwent appendectomy for appendicitis at our tertiary care center. Patients with an appendiceal tumor on their final pathology report were compared to patients with no tumor. Conditions present on admission were used to create a multivariate logistic regression model to predict appendiceal tumor. Risk factors were reported as odds ratio (OR) [95% confidence interval]. Model strength was assessed by area under the receiver operating characteristic curve (AUROC).

Results—Seventeen patients (2.5%) had an appendiceal tumor. Within this group, fourteen underwent immediate appendectomy, two initially had non-operative management but failed to improve on antibiotics and underwent appendectomy during the initial admission, and one had successful non-operative management and elective appendectomy 19 days after discharge. Four variables contributed to the multivariate model to predict the presence appendiceal tumor: age ≥50 (OR 3.6 [1.1–11.4]), outpatient steroid/immunosuppressant use (OR 12.1 [2.0–72.5]), the absence of migratory right lower quadrant pain (OR 4.7 [1.2–18.1]), and the appearance of a phlegmon on CT scan (OR 7.0 [1.6–30.2]); model AUROC: 0.860 [0.705–0.969].

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Conclusions—For patients presenting with acute appendicitis, conditions present on admission may predict underlying appendiceal tumor. Patients with advanced age, multiple comorbidities, atypical presentation, and complicated appendicitis should be considered for appendectomy during the index admission or at earliest convenience if non-operative management is necessary.

Level of evidence—level III prognostic study

Keywords

appendicitis; appendectomy; tumor; cancer; risk factors

Introduction

As non-operative management of appendicitis gains popularity (1–3), identification of patients who are at increased risk for appendiceal tumors becomes increasingly important. Data from the National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) project demonstrate 5-year survival ranging from 93% for carcinoid tumors to 55% for colonic-type adenocarcinoma and 27% for signet ring adenocarcinoma (4). The age-adjusted incidence of appendix cancer was only 0.12 cases per 1 million people per year, accounting for less than 0.5% of all gastrointestinal malignancies (5). Although appendiceal tumors are rare, the lifetime incidence of acute appendicitis is about 7.7% in the United States (6). Therefore, appendiceal tumors are commonly found incidentally on appendectomy specimens from patients who presented with acute appendicitis. The incidence of appendiceal tumor on appendectomy specimens from patients who presented with acute appendicitis ranges from 0.9%–1.7% (7, 8).

Non-operative management of acute appendicitis may increase the likelihood that patients are subjected to longer delays in the diagnosis of underlying appendiceal cancer. Within the last four years, three institutions (9–11) have reported alarmingly high rates of appendiceal tumors (12.4%, 27.7%, and 29.4%) found incidentally on interval appendectomy specimens from patients who presented with acute appendicitis and were initially treated with non-operative management. This scenario may be avoided if patients at increased risk for appendiceal cancer could be identified when they first present with appendicitis. Several studies (9–11) have identified advanced age as a risk factor for appendiceal cancer. Unfortunately, patient age lacks sensitivity and specificity, and the relative importance of other risk factors are unclear, though several candidates have been identified: female gender (12), appendiceal perforation (12), Crohns disease (13), longer duration of symptoms (14), and anemia on admission (14).

The purposes of this study were to identify conditions present on admission that are associated with the incidental finding of an appendiceal tumor following appendectomy for appendicitis and to use these variables to generate a clinical prediction model. We hypothesized that among patients presenting with acute appendicitis, those with advanced age, multiple comorbidities, atypical presentation, and complicated appendicitis would be more likely to have underlying appendiceal tumors.

Methods

We performed a retrospective cohort analysis of 677 consecutive adult patients (age ≥ 18 years) who underwent appendectomy for acute appendicitis at our tertiary care academic center during a 4-year period ending 7/1/2016. Institutional Review Board approval was obtained. Pregnant women and patients who had received chemotherapy or radiotherapy within 90 days were excluded. Data regarding patient demographics, comorbidities, clinical presentation, systemic inflammatory response syndrome criteria (15), the modified Alvarado score (16–18), computed tomography (CT) imaging findings (19), operative findings, pathology findings, tumor stage (20), and outcomes within 90 days were obtained from our institutional data repository and review of the electronic medical record.

The primary outcome was the incidental finding of an appendiceal tumor on the final pathology report. Patients with an appendiceal tumor were compared to patients with no tumor. Continuous variables were compared by the Kruskal-Wallis test and reported as median [interquartile range]. Discrete variables were compared by Fisher's Exact test and reported as n (%). Conditions present on admission that were significantly different ($p < 0.05$) between groups were assessed for the ability to predict the presence of an appendiceal tumor on univariate logistic regression. Cutoff values for continuous variables were determined by Youden's index, coordinating points on the receiver operating characteristic curve to identify a value with high sensitivity and reasonable specificity for predicting appendiceal tumor (21). Variables were selected for inclusion in the multivariate model based on clinical relevance and collinearity to other variables, assessed by Pearson's r. Model strength was assessed by calculating the area under the receiver operating characteristic curve. Statistical analysis was performed in SPSS (version 23, IBM, Armonk, NY).

Results

Study population

Seventeen patients (2.5%) presented with acute appendicitis and were found to have an appendiceal tumor; 660 patients had no tumor. Baseline characteristics for both groups are listed in Table 1. Patients with a tumor were older (53 vs. 30 years, $p = 0.001$), had higher American Society of Anesthesiologists class and Charlson comorbidity index scores, and were more likely to have an outpatient prescription for chronic steroid or immunosuppressant medications. A greater proportion of patients with a tumor were female, though the difference was not statistically significant (71% vs. 49%, $p = 0.089$). Systemic inflammatory response syndrome criteria were similar between groups. Modified Alvarado scores were one point lower in patients with tumor (6.0 vs. 7.0, $p = 0.074$), a difference that was primarily attributable to the observation that patients with a tumor were less likely to present with classic migratory right lower quadrant pain (24% vs. 63%, $p = 0.002$). On subgroup analysis, admission hemoglobin was significantly lower among patients with tumor stage II or greater (n=10) compared to all other patients (13.6 vs. 14.2 g/dL, $p = 0.048$).

Diagnostic findings

Findings on admission computed tomography (CT) scan, operative exploration, and pathologic examination of the appendectomy specimen are listed in Table 2. Findings from CT scans performed at an outside facility (n = 3 for the tumor group, n = 59 for the no tumor group) were not consistently reported and were not included in the analysis. Appendiceal diameter was one millimeter greater in patients with a tumor, a difference that was not statistically significant (12 vs. 11 mm, $p = 0.060$). CT scan evidence of a phlegmon was more frequent in the tumor group (21% vs. 4%, $p = 0.013$). Suspicious masses were identified on CT scans for three patients in the tumor group (21%) and two patients in the no tumor group (0.3%, $p < 0.001$). All five masses seen on CT scan were also visualized intraoperatively. Suspicious masses were identified in the operating room for six patients in the tumor group and two patients in the no tumor group ($p < 0.001$). Ileocecectomy was the index operation for one patient in the tumor group and eight patients in the no tumor group; right hemicolectomy was the index operation for four patients in the tumor group and five patients in the no tumor group. For all cases in which ileocecectomy or right hemicolectomy was performed in the absence of an apparent mass, it was noted that inflamed, friable tissue was extending onto the base of the cecum, and was deemed unsuitable for a staple line.

Outcomes

Hospital length of stay was significantly longer in the tumor group (3.0 vs. 1.2 days, $p = 0.039$). At the time of discharge, patients with appendiceal tumors had lower white blood cell counts (8.3 vs. 9.8 $\times 10^9$/L, $p = 0.040$) and hemoglobin levels (12.1 vs. 13.0 g/dL, $p = 0.024$). Although rates of infectious complications were similar between groups (6% vs. 6%, $p > 0.999$), patients with appendiceal tumor were more likely to be readmitted within 90 days (35% vs. 6%, $p = 0.001$), which was attributable to oncologic status. Of the six patients in the tumor group who were readmitted within 90 days, five were readmitted for right hemicolectomy, and one was readmitted for drug-induced angioedema.

Of the 17 patients with appendiceal tumors, 16 underwent appendectomy during the initial admission; one patient initially had non-operative management and underwent interval elective appendectomy 19 days after discharge. Two of the 16 patients who underwent appendectomy during their initial admission had a trial of non-operative management, but did not respond to antibiotic therapy and required appendectomy 23 and 94 hours after admission. On final pathology reports, there were seven pre-malignant tumors (four carcinoids and three goblet cell carcinoids) and 10 malignant tumors (five adenocarcinomas, two mucinous adenocarcinomas, one signet ring adenocarcinoma, one adenosquamous carcinoma, and one B-cell lymphoma) with stages as follows: stage I: n = 7, stage II: n = 3, stage III: n = 5, stage IV: n = 2. Six patients with an appendiceal tumor had previous colonoscopies. For two of these patients, colonoscopy was performed within four months of appendectomy, but the bowel preparation was poor, and the base of the cecum was not adequately visualized. The other four colonoscopies were performed 91 days (0.5 cm tumor), 281 days (3.0 cm tumor), 2.5 years (1.0 cm tumor), and 9.6 years (4.0 cm tumor) before appendectomy, and no cecal polyps or masses were visualized. There were five patients age 50 or greater with an appendiceal tumor that never had a colonoscopy. In this

group of patients, tumor sizes were 1.5, 3.5, 4.5, 10.0, and 11.0 cm. Four of these patients had stage III appendix cancer and one patient had stage IV appendix cancer.

Prediction model

Eight variables that were significantly different between groups are listed as univariate predictors of appendiceal tumor in Table 3. Four of these eight variables were excluded from the multivariate model. ASA physical status classification ≥3 was collinear with age (r = 0.525, $p < 0.001$) and steroid/immunosuppressant use (r = 0.109, $p = 0.005$). Charlson comorbidity index ≥3 was also collinear with age (r = 0.282, $p < 0.001$) and steroid/immunosuppressant use (r = 0.123, $p = 0.001$). Former smoker status was excluded because the greater proportion former smokers in the tumor group (35% vs. 15%, $p = 0.040$) was partially offset by a greater proportion of active smokers in the no tumor group (20% vs. 12%, $p = 0.548$), such that patients in the tumor group may have been more likely to have quit smoking because they were older. This interpretation is supported by the observed collinearity between former smoker status and age (r = 0.247, $p < 0.001$). Finally, the presence of a suspicious mass on CT scan was excluded because this finding alone sufficiently raises suspicion for tumor, obviating the need for a model to predict the presence of a tumor.

The remaining four variables each contributed significantly to the multivariate model: age ≥50 (OR 3.6 [1.1–11.4]), outpatient steroid/immunosuppressant use (OR 12.1 [2.0–72.5]), the absence of migratory right lower quadrant pain (OR 4.7 [1.2–18.1]), and the appearance of a phlegmon on CT scan (OR 7.0 [1.6–30.2]). The multivariate model correctly classified 97.9% of all cases, and had area under the receiver operating characteristic curve 0.860 (95% CI 0.705–0.969) with sensitivity 92.3% and specificity 59.9% for predicting appendiceal tumor.

Discussion

Our findings suggest that several factors are associated with appendiceal tumors among patients presenting with acute appendicitis. Consideration of these risk factors may help to avoid the scenario in which a patient with a pre-malignant or malignant tumor is allocated to non-operative management followed by a long delay before interval elective appendectomy, or worse: the patient seeks no further medical care until the tumor has progressed, manifested by bleeding, obstruction, or carcinomatosis.

To our knowledge, we report the first multivariate prediction model for appendiceal tumor. However, our findings are consistent with previous reports, which have identified age advanced age and complicated appendicitis as risk factors for the presence of an appendiceal tumor (9–11). Although the proportion of females in the tumor group was not significantly higher, this study may have been underpowered to detect a true difference, as observed by Sadot et al (12). The same explanation may apply to the association between Crohns disease and appendiceal tumor, as observed by West et al (13). Although admission hemoglobin was not significantly lower among patients with appendiceal tumor compared to patients with no tumor, subgroup analysis demonstrated that patients with stage II or greater tumors did have significantly lower hemoglobin on admission, consistent with data from Todd et al (14).

Notably, most tumors were not identified on preoperative CT. This may have been because many tumors were small, tumors lacking calcifications may have been difficult to distinguish from an inflammatory mass, and even carcinoid tumors may be hypovascular in up to 20% of all cases (22, 23). Finally, although patients who had received chemotherapy or radiotherapy within 90 days were excluded from our study, it should be noted that patients with a known cancer who present with appendicitis may be at increased risk for appendiceal malignancy (24).

This study is limited by its retrospective design, small sample size (n=677), and lack of long-term follow up. The selection bias inherent to retrospective studies was limited as much as possible by including all consecutive patients who met relatively broad inclusion criteria. Although sample size is a limiting factor, the small number of patients in this study allowed for a reasonable degree of granularity by supplementing data repository parameters with a detailed review of the electronic medical record. Validation in a large, prospective, multi-center dataset would be necessary to avoid overfitting and ensure broad generalizability. Ideally, prediction models should be validated in a sample size containing at least 100 events and 100 non-events (25, 26). Assuming that appendiceal tumors will be found on approximately 1.3% of all appendectomy specimens from patients presenting with appendicitis (7, 8), robust validation of this model would require a series of 7,692 appendectomies (7, 8). This endeavor may help to ensure the appropriate application of non-operative management and emphasize the importance of early interval appendectomy for patients at increased risk for appendiceal tumor.

Conclusions

Conditions present on admission may accurately predict the presence of an appendiceal tumor for patients presenting with acute appendicitis. Independent risk factors include advanced age, outpatient steroid/immunosuppressant use, the absence of migratory right lower quadrant pain, and the appearance of a phlegmon on CT scan. Patients with these risk factors should be advised to undergo appendectomy at the index admission or at earliest convenience if non-operative management is necessary. These findings should be validated in a large, prospective, multi-center dataset.

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Table 1

Baseline characteristics for the study population.

Patient characteristics	Tumor (n = 17)	No tumor (n = 660)	*p*
Age	53 [35–61]	30 [22–45]	0.001
Female	12 (71%)	323 (49%)	0.089
ASA physical status classification	2.0 [2.0–3.0]	2.0 [1.0–2.0]	0.023
Charlson comorbidity index	1.0 [0.0–4.5]	0.0 [0.0-0.0]	<0.001
Crohns disease	1 (6%)	2 (0.3%)	0.074
Diabetes	3 (18%)	35 (5%)	0.064
Without complications	2 (12%)	29 (4%)	0.180
With complications	1 (6%)	6 (1%)	0.164
Steroid/immunosuppressant use	2 (12%)	11 (2%)	0.039
Body mass index	29.7 [23.8–32.6]	25.8 [22.6–30.0]	0.161
Former smoker	6 (35%)	102 (15%)	0.040
Current smoker	2 (12%)	130 (20%)	0.548
On admission			
Duration of symptoms (hours)	17 [8–66]	23 [12–45]	0.780
T_{max} within 6 hours	36.9 [36.8–37.3]	37.0 [36.8–37.3]	0.394
T_{min} within 6 hours	36.7 [36.5–36.9]	36.8 [36.5–37.0]	0.557
Heart rate	80 [75–102]	86 [74–98]	0.764
Respiratory rate	16 [15–18]	16 [16–18]	0.303
White blood cell count ($\times 10^9$/L)	14.5 [9.0–18.0]	13.8 [10.7–16.8]	0.955
% neutrophils	86.0 [69.6–90.0]	81.8 [75.0–87.5]	0.339
SIRS	5 (29%)	214 (32%)	>0.999
Absolute neutrophil count ($\times 10^9$/L)	12.8 [4.7–15.9]	11.2 [8.1–14.3]	0.831
Absolute lymphocyte count ($\times 10^9$/L)	1.2 [0.7–1.7]	1.4 [1.0–2.0]	0.192
Neutrophil:lymphocyte ratio	8.9 [3.5–20.7]	8.1 [4.6–13.6]	0.773
Hemoglobin (g/dL)	13.7 [13.0–14.4]	14.2 [13.1–15.2]	0.175
Alvarado score	6.0 [4.0–7.0]	7.0 [6.0–7.0]	0.074
Migratory RLQ pain	4 (24%)	416 (63%)	0.002
Anorexia	15 (88%)	627 (95%)	0.218
Nausea or vomiting	10 (59%)	501 (76%)	0.148
RLQ tenderness	17 (100%)	651 (99%)	>0.999
Rebound tenderness	7 (41%)	242 (37%)	0.800

ASA: American Society of Anesthesiologists, SIRS: systemic inflammatory response syndrome, RLQ: right lower quadrant. Data are presented as median [interquartile range] or n (%).

Table 2

Findings on admission computed tomography (CT), operative exploration, and pathologic examination.

Findings	Tumor (n = 17)	No tumor (n = 660)	*p*
CT scan findings			
Had a CT scan	17 (100%)	656 (99%)	>0.999
CT performed at OSH[†]	3 (18%)	59 (9%)	0.198
Intravenous contrast study	13 (93%)	568 (95%)	0.510
Fat stranding	11 (79%)	477 (80%)	>0.999
Right lower quadrant fluid	7 (50%)	180 (30%)	0.141
Appendicolith	4 (29%)	195 (33%)	>0.999
Appendix diameter (mm)	12 [11–14]	11 [9–13]	0.060
Wall thickening	4 (29%)	126 (21%)	0.510
Mural enhancement	2 (14%)	233 (39%)	0.092
Phlegmon	3 (21%)	22 (4%)	0.013
Abscess	0	23 (4%)	>0.999
Suspicious mass	3 (21%)	2 (0.3%)	<0.001
Operative findings			
Suppuration	4 (24%)	94 (14%)	0.290
Necrosis or gangrene	2 (12%)	68 (10%)	0.692
Perforation	5 (29%)	106 (16%)	0.176
Suspicious mass	6 (35%)	2 (0.3%)	<0.001
Pathology findings			
Appendicitis	15 (88%)	641 (97%)	0.094
Suppuration	2 (11%)	89 (13%)	>0.999
Necrosis or gangrene	4 (24%)	110 (17%)	0.507

[†]Findings from outside hospital (OSH) CT scans were not consistently reported and were not included in the analysis. Data are presented as n (%) or median [interquartile range].

Table 3

Univariate and multivariate predictors of appendiceal tumor.

Factors	Univariate regression			Multivariate model*		
	OR	95% CI	*p*	OR	95% CI	*p*
Age ≥50	5.9	2.2–15.9	<0.001	3.6	1.1–11.4	0.032
ASA physical status classification ≥3[a]	3.4	1.3–9.1	0.015	-	-	-
Charlson comorbidity index ≥3[b]	16.8	5.3–53.2	<0.001	-	-	-
Steroid/immunosuppressant use	7.9	1.6–38.6	0.011	12.1	2.0–72.5	0.006
Former smoker[c]	3.0	1.1–8.2	0.035	-	-	-
Absence of migratory RLQ pain	5.5	1.8–17.2	0.003	4.7	1.2–18.1	0.023
Phlegmon on CT scan	7.8	1.0–30.5	0.003	7.0	1.6–30.2	0.009
Suspicious mass on CT scan[d]	70.5	10.9–456	<0.001	-	-	-

OR: odds ratio, CI: confidence interval, ASA: American Society of Anesthesiologists, RLQ: right lower quadrant, CT: computed tomography.

[a–d]Excluded from the multivariate prediction model for the following reasons: [a]collinearity with age and steroid/immunosuppressant use; [b]collinearity with age and steroid/immunosuppressant use; [c]collinearity with age; [d] the presence of a mass on CT scan obviates the need for a prediction model.

*Area under the receiver operating characteristic curve: 0.860 (95% CI 0.705–0.969).