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Risk Factors for Appendiceal Cancer After Appendectomy

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Abstract

Background: Appendiceal cancer (AC) is a rare malignancy usually diagnosed incidentally after appendectomy. Risk factors for AC are poorly understood. We sought to provide a descriptive analysis for patients with AC discovered after appendectomy for acute appendicitis (AA).

Methods: The 2016-2017 American College of Surgeons-National Surgical Quality Improvement Program Procedure-Targeted Appendectomy database was queried for adult patients who underwent appendectomy for image-suspected AA. Patients with pathology consistent with AA were compared to patients found to have AC. A multivariable logistic regression model was used for analysis.

Results: From 21 058 patients, 203 (1.0%) were found to have AC on pathology. Compared to patients with AA, patients with AC were older (median, 48 vs. 40 years old, $P < .001$). The AA group had a similar rate of perforated appendix compared to the AC group (16.3% vs. 13.4% $P = .32$). After adjusting for covariates, associated risk factors for AC were: age ≥65 years old (odds ratio (OR) 2.25, 1.5-3.38, $P < .001$), absence of leukocytosis (OR 1.58, 1.16-2.17, $P = .004$), and operative time ≥1 hour (OR 1.57, 1.14-2.16, $P = .006$). Gender, race, and history of smoking were not independent associated risk factors for AC.

Conclusion: The incidence of AC after appendectomy for suspected AA is approximately 1% in a large national analysis. These factors may be used to help identify patients at higher risk for AC after appendectomy.

Keywords
appendiceal cancer, acute appendicitis, appendectomy, general surgery

Introduction

Appendectomy is one of the most common general surgery procedures with over 400 000 cases performed in the United States annually.[1] Appendiceal cancer (AC) is a rare neoplasm that is often diagnosed incidentally in pathologic evaluation after an appendectomy. It may also be diagnosed via abdominal imaging or at the appendiceal orifice during colonoscopy.[2] The diagnosis of AC is an important distinction from acute appendicitis (AA) because preoperative, intraoperative, and postoperative management greatly differs. Furthermore, the rate of AC has been reported to be between .7 and 1.7% incidentally after appendectomy.[3-7]

There have been several recent randomized controlled trials that support nonoperative management (NOM) of noncomplicated AA.[8-10] However, the risk of AC is a concern for any patient who does not undergo an appendectomy since AC is associated with considerable mortality. In fact, a large series of malignant appendiceal tumors derived from the Surveillance, Epidemiology, and End Results database, including mucinous adenocarcinoma, colonic adenocarcinoma, adenocarcinoid, malignant carcinoid, and signet ring cell, had a 5-year survival of 58%, 55%, 81%, 93%, and 27%, respectively.[11,12] Despite advances in imaging, 50% of ACs are being diagnosed incidentally after appendectomy.[3] Due to the low incidence and wide variety of histology subtypes,

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there has been little epidemiological investigation or consensus on risk factors for AC.[2] Suggested risk factors from retrospective series include age ≥40 years-old, complicated appendicitis, periappendiceal abscess, atypical presentation, and appendiceal width on imaging.[13-15]

Although a rare tumor, the incidence of AC has increased more than 50% over the past several decades and thus further understanding of this malignancy is needed.[16] Furthermore, with the increasing use of NOM of AA, the risk of a missed AC needs to be considered. Therefore, we sought to identify risk factors for AC in patients presenting with image-suspected AA.

Methods

This study was approved by our institutional review board. We performed a retrospective analysis of the American College of Surgeons–National Surgical Quality Improvement Program (ACS-NSQIP) Procedure-Targeted Appendectomy database between January 2016 to December 2017. All adult patients ≥18 years of age with evidence of AA on preoperative imaging who underwent an appendectomy were included. Imaging modalities included ultrasound, computed tomography, and magnetic resonance imaging. The primary outcome was evidence of AC on final pathology, which is defined in the NSQIP data dictionary as tumor/malignancy involving the appendix with or without appendicitis. Two groups were compared: patients with and without AC. Demographic information collected included age, sex, ethnicity, preoperative white blood cell (WBC) count, and medical comorbidities such as congestive heart failure, chronic obstructive pulmonary disease, diabetes, hypertension, smoking status, steroid use, and preoperative weight loss. Intraoperative details such as surgical approach (open vs. laparoscopic), intraoperative findings (perforation or abscess), and operative time were collected. Outcome measures that were collected included length of stay (LOS), 30 day postoperative abscess formation, readmission rate, and mortality.

All variables were coded as present or absent. Descriptive statistics were performed for all variables. A Student's t-test or Mann-Whitney U test was used to compare continuous variables and chi-square was used to compare categorical variables for bivariate analysis. Categorical data were reported as percentages, and continuous data were reported as medians with interquartile range or as means with standard deviation. A multivariable stepwise forward hierarchical logistic regression model was used for analysis. Chosen based on a discussion among authors and a review of the literature, covariates included age ≥65 years, history of smoking, wound contamination, American Society of Anesthesiologists Physical Status (ASA-PS) classification ≥3,

Table 1. Demographics of Patients Undergoing Appendectomy Stratified by Pathology.

Characteristic	Appendicitis (n = 20855)	Appendiceal cancer (n = 203)	*P*-value
Age, year, median (IQR)	40 (26, 52)	48 (33, 62)	<.001
Male, n (%)	10811 (51.8%)	96 (47.3%)	.197
ASA-PS classification, n (%)			<.001
1	6301 (30.2%)	42 (20.7%)	
2	11086 (53.2%)	105 (51.7%)	
3	3174 (15.2%)	51 (25.1%)	
4	247 (1.2%)	5 (2.5%)	
5	3 (<.1%)	0	
Race, n (%)			.559
White	13012 (62.4%)	138 (68.0%)	
Black	1622 (7.8%)	15 (7.4%)	
Asian	913 (4.4%)	7 (3.4%)	
Hispanic, n (%)	2441 (13.8%)	14 (8.2%)	.035
Comorbidities, n (%)			
Congestive heart failure	56 (.3%)	2 (1.0%)	.053
COPD	217 (1.0%)	4 (2.0%)	.196
Hypertension	3328 (16.0%)	60 (29.6%)	<.001
Smoker	3322 (15.9%)	26 (12.8%)	.226
Diabetes	1053 (5.0%)	17 (8.4%)	.032
Chronic steroid use	300 (1.4%)	3 (1.5%)	.963
Weight loss	36 (.2%)	0 (.0%)	.554

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ASA-PSs, American Society of Anesthesiologists Physical Status.

Table 2. Laboratory, Imaging, and Intraoperative Findings After Appendectomy Stratified by Pathology.

Characteristic	Appendicitis (n = 20855)	Appendiceal cancer (n = 203)	*P*-value
Wound classification, n (%)			.002
Clean/contaminated	4068(19.5%)	60(29.6%)	
Contaminated	11118(53.3%)	86(42.4%)	
Dirty/infected	5326(25.5%)	54(26.6%)	
Absence of leukocytosis, n (%)	6968(33.9%)	96(48.7%)	<.001
Preoperative WBC count, median (IQR)	13.0(9.9, 15.8)	11.5(7.9, 14.6)	<.001
Operative approach			.027
Laparoscopic	19791(94.9%)	180(88.7%)	
Laparoscopic w/open assist	103(.5%)	4(2.0%)	
Laparoscopic w/unplanned open conversion	373(1.8%)	8(3.9%)	
Open (planned)	563(2.7%)	11(5.4%)	
Intraoperative findings, n(%)			.321
Perforation and abscess	1562(7.5%)	20(9.9%)	
No perforation or abscess	15682(75.2%)	143(70.4%)	
Abscess only	826(4.0%)	7(3.4%)	
Perforation only	2785(13.4%)	33(16.3%)	
Operative time (min), median (IQR)	53(34, 64)	68(39, 88)	.001
Specimen placed in bag prior to removal, n (%)	18475(88.6%)	165(81.3%)	.004

Abbreviations: WBC, white blood cell; IQR, interquartile range; CT, computed tomography.

Hispanic ethnicity, WBC count ≤11, sex, and operative time >1 hour.[13-15,17] We then adjusted for these covariates in a hierarchical multivariable logistic regression model, and the adjusted risk for AC was reported with an OR and 95% confidence intervals (CIs). All *P*-values were two-sided, with a statistical significance level of <.05. All analyses were performed with IBM SPSS statistics for Windows (version 24, IBM Corp, Armonk, New York).

Results

Demographics

There was a total of 21 058 patients identified who underwent an appendectomy for image-suspected AA during our study period. A total of 203 (1.0%) were found to have AC on pathology and 20 855(99.0%) had AA (Table 1). When comparing the AC cohort to the AA cohort, there was no difference in male sex (47.3% vs. 51.8%, *P* = .19). However, when compared to the AA cohort, the AC cohort had a decreased incidence of Hispanics (8.2% vs. 13.8%, *P* = .035). Patients diagnosed with AC were older (median, 48 vs. 40 years old, *P* < .001) and had more medical comorbidities such as hypertension (29.6% vs. 16.0%, *P* < .001) and diabetes (8.4% vs. 5%, *P* = .032) (Table 1).

Diagnostic and Operative Findings

Patients with AC were more likely to have an absence of leukocytosis (48.7% vs. 33.9%, *P* < .001), require an open surgery (9.3% vs. 4.5%, *P* = .027), and have a longer operative time (68 minutes vs. 53 minutes, *P* < .001) than patients with AA. There was no difference in intra-operative findings of perforation or abscess (29.6% vs. 24.8%, *P* = .32) between the cohorts (Table 2). On multivariable analysis, associated risk factors for AC were: age ≥65 years old (OR 2.25, 1.5-3.38, *P* < .001), absence of leukocytosis (OR 1.58, 1.16-2.17, *P* = .004), and operative time ≥1 hour (OR 1.57, 1.14-2.16, *P* = .006). After adjusting for covariates, ASA-PS classification, sex, ethnicity, and smoking history (all *P* > .05) were not independent risk factors for AC in patients with image-suspected AA who underwent appendectomy (Table 3).

Table 3. Multivariable Logistic Regression Analysis for Risk of Appendiceal Cancer After Appendectomy.

Risk factor	OR	CI	*P*-value
Age≥65 years old	2.25	1.5-3.38	<.001
ASA-PS classification >3	1.28	.86-1.89	.222
Hispanic	.65	.38-1.13	.129
Absence of leukocytosis	1.58	1.16-2.17	.004
Male	1.10	.80-1.50	.560
Operative time≥1 hour	1.57	1.14-2.16	.006
Smoking	.90	.63-1.29	.577

Abbreviations: ASA-PS, American Society of Anesthesiologists Physical Status; OR, odds ratio; CI, confidence interval.

Clinical Outcomes

Patients with AC had a longer LOS, were more likely to be readmitted within 30 days (6.9% vs. 3.6%, *P* = .02), and

Table 4. Clinical Outcomes of Patients Undergoing Appendectomy Stratified by Pathology.

Outcome	Appendicitis (n = 20855)	Appendiceal cancer (n = 203)	*P*-value
LOS, days, median (IQR)	1(1, 2)	1(1, 3)	.006
Postoperative intra-abdominal abscess, n (%)	688(3.3%)	4(2.0%)	.914
Any 30 day readmissions	750(3.6%)	14(6.9%)	.021
Mortality, n (%)	16(.1%)	1(.05%)	.038

Abbreviations: LOS, length of stay; IQR, interquartile range.

had a lower mortality (.05% vs. .1%, P = .038) than patients with AA. There was no significant difference found in postoperative abscess between the 2 cohorts (2.0% vs. 3.3%, P = .91) (Table 4).

Discussion

AC is a known incidental finding after performing an appendectomy for AA, and our study suggests several factors are associated with this finding. Our study reported an incidence of 1.0% for AC after appendectomy for image-suspected AA. In addition, we found that age ≥65 years old was associated with more than double the risk of AC. Additionally, we found lack of leukocytosis and longer operative time were associated with increased risk of AC. Whereas sex, ethnicity, and smoking were not associated with risk of AC in patients undergoing appendectomy with suspected AA.

The management of AA has had a recent shift toward NOM for noncomplicated appendicitis.[8-10,15] However, many of the studies that purport NOM fails to highlight the risk of missing AC, which in our study was 1% of the entire population of patients suspected to have AA. This is consistent with other studies which have reported incidences ranging from .7 to 2.3%.[3-7,15] Furthermore, we identified potential preoperative risk factors that could be used to help stratify patients or help to guide clinical decision-making, such as age ≥65 years and a lack of leukocytosis as predictors of AC. Many previous studies have also found age to be a risk factor for AC.[4,14,17,18] For instance, Westfall et al found that for every year increase in age there was a 1.03 (95% CI 1.01, 1.06) increase in odds of having AC. In addition, Loftus et al found in their multivariable regression analysis that age ≥50 years was associated with AC.[14]

In regards to the lack of leukocytosis, to date, this is the first study to show this as an associated risk factor. This finding is supported by Todd et al, they showed that 64% of AC patients with suspected AA had a normal WBC on presentation.[19] These generalized signs of inflammation and classic presentation of AA may be less common in AC. Loftus et al demonstrated that AC was associated with an atypical presentation of AA, in their study, migratory right lower quadrant pain was less common in patients with AC.[14] Therefore, our study supports a heightened awareness for clinical providers for AC in any patient of 65 years or above and/or with absence of leukocytosis. These findings should especially be helpful if any consideration for NOM is being entertained.

Smoking has previously been demonstrated to be associated with multiple gastrointestinal malignancies including esophageal, gastric, pancreatic, and colorectal cancer.[20-24] However, in our large national analysis, smoking was not associated with AC. This is consistent with some other studies.[13,14] In addition, we found other factors such as race and sex were also not associated with risk of AC for image-suspected AA.

This was a large retrospective database study and thus has inherent limitations such as reporting bias, missing data, and misclassifications. In addition, we only included appendectomy for image-suspected AA, and thus do not provide a complete epidemiologic evaluation of AC. Furthermore, we do not have data on patients undergoing an interval appendectomy and some evidence shows that this group is at an even higher risk of AC.[4] Also, this database is missing pertinent data variables such as family history of gastrointestinal malignancies, the patient's prior oncologic history, and whether the patient has had a prior colonoscopy. This database also does not provide information regarding long-term outcomes, including oncological treatment and overall survival. Despite these limitations, the strength of our study is the large sample size and it is not limited to a single center or region. This is one of the first large retrospective studies looking at risk factors associated with AC at the time of appendectomy for image-suspected AA.

Conclusion

The incidence of AC after appendectomy for image-suspected AA was 1% in a large contemporary national analysis spanning 2 years of data. Associated risk factors for AC in patients undergoing appendectomy for image-suspected AA include age ≥65 years, absence of leukocytosis, and longer operative time. These risk factors should be validated in future prospective studies and with the addition of other novel risk factors may be used to help identify and counsel patients at higher risk for AC who present with AA. Furthermore, the authors believe that they should be incorporated into any decision to perform NOM of AA.

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.

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